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PRESIDENTIAL ADDRESS

THE IDEALS, RESPONSIBILITIES, AND REWARD OF THE OBSTETRICIAN*

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TO BE privileged to serve as your presiding officer is the highest professional honor which has ever been conferred upon me. For this evidence of your confidence and kindness let me express my appreciation and thanks. I cannot but feel very humble and unworthy when contemplating the stature of those whom the Association has so honored in the yesteryears.

This association has been a never-ending inspiration to me since the first meeting it was my privilege to attend, in September, 1923, as a guest. To me it was a most remarkably enjoyable experience to be welcomed into an atmosphere of such friendly comradeship.

Then to listen to the vigorous discussions of the addresses and papers, at times approaching the acrimonious in their earnestness; yet always constructive, fair, and in friendship, even though so heated. One of that meeting's visitors returned to his work stimulated beyond measure, and with an earnest ambition and determination to be worthy of such friends as these.

Over the years, this Association has continued as an inexhaustible source of help in those periods which come to all men of our profession, when enthusiasm and morale are at a low tide and we wonder, "Oh! What's the use?" Could one give up in surrender with the friendly spirits of such a galaxy of Fellows, past and present, assembled in Memory's halls? For many of the ac-

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complishments and successes, small though they may be, which have come to me, I salute our Association and its Fellowship.

It is but natural that one should debate with himself and wonder if he has a message to bring to you in the time-honored address of the President which is expected at the Annual Meeting and which it is the custom for him to deliver. One of the self-imposed duties of most presidents-elect, I suspect, is to read the mental masterpieces of his predecessors in this honored position. A number of those who have occupied this office have dwelt upon some particular phase of their own work and professional interest. Many of them were, at the time delivered, revolutionary and of epoch-making importance in the future development of the field of our Association's professional endeavors.

The accomplishments of this Association in the field of maternal and child welfare—prenatal, natal, and postnatal—are outstanding. Fellows of the Association have done yeoman service in developing the American Board of Obstetrics and Gynecology and in the organization of the Advisory Council of the Medical Specialty Boards. Most of the Fellows of the Association are teachers in the specialty. To them we must look for the training, in our medical colleges, of the professional personnel of the years to come, not only the specialists but the general practitioners as well.

To one whose professional life span covers more than four decades of active work, it would seem well to discuss some of the problems facing the medical profession at the moment. Possibly we may profit by making an inventory not only of the "stock-on-hand," so to speak, but also of the quality of the finished product now being delivered for the use of the sick, our clientele. Never during my time in the profession has medicine, general practice and specialties alike, been under such a stress of attack from so many sources as it is at the present moment.

It is not my purpose to discuss the cost of medical care today, the distribution of physicians or the merits of voluntary health insurance rather than the compulsory measures at the moment advocated by those in high authority. While these are of transcendent importance in the economics of our citizenry, including us physicians, it is not felt that this is the forum where such a discussion should be staged.

It seems that seldom today is the practice of medicine ever thought of as a profession and, as such, as being both an art and a science. At times one is inclined to feel that it is in danger of being regarded as a trade and becoming a commercialized source of livelihood. One wonders if the old apprenticeship and preceptor method of medical teaching, long since abandoned, did not, after all, impart most important qualifications which a physician should possess and which are not only a knowledge of medicine in itself. Such are character, sympathy, industry, charity, patience, economics, exalted ideals, and a spirit of service to one's fellows. The scientifically high-pressured medical curriculum of today has no place for these, consequently they are not taught effectively there or elsewhere. One is at a loss to discover if anything has been provided to take the place of this cultural development. The carefully trained, scientifically

stuffed, assembly-line produced physicians of today are woefully lacking in their knowledge of the humanities, of the art of medicine, if you will. The immortal Osler was superendowed with a knowledge of the humanities and of the science of medicine. One wonders if it were not his humanity rather than his scientific attainments which so endeared him to his disciples and patients.

In the final analysis the art of medicine is but an understanding of the patient as a functioning whole, of his thoughts and feelings under the stress of illness, and the technique by which we bring our scientific knowledge and skill to the treatment of his present disease. It has been said, "Art runs for the stomach pump, while science studies the phenomena of the poisoning." Physicians of the generations before us were masters of the art of medicine even though their science may have been somewhat lacking. They did not know it is such but they were uncertified Diplomates of the Specialty Board of Psychosomatic Medicine.

I quote from the address of President Charles A. L. Reed at the Annual Meeting of this Association fifty years ago. "The characteristic of the present era, one that distinguishes it from former civilizations, is that the process of specialization is never carried to the point of complete segmentation. Each specialty, however assiduously cultivated, remains an integral part of the great general profession, the masters of which must ever stand as our ideals.

"All specialists today are primarily the products of general medical culture. The act of specialization takes place after, and not before, entrance into the general profession. When this order is changed, then comes the day of danger."

Can it be that this day approaches? Are the present-day graduates trained with the basic idea that they are preparing primarily to be physicians? It is only by personal practical experience that recently graduated young physicians will learn to use the tools of their profession, the scientific knowledge imparted to them during the undergraduate and intern years, in caring for the ill persons who may consult them.

Most of us, especially those who may have received our diplomas in the early years of the present century, and who settled in one of the smaller cities where hospital facilities were meager or by present-day standards nonexistent, can recall many incidents where emergencies fraught with catastrophic possibilities were encountered in the homes of our patients. Is it possible to forget that appalling sense of helplessness we experienced when confronted with the ruptured uterus of a woman at term, before the day of blood-typing and cross-matching, Rh-factor determinations, blood banks, or plasma? Would physicians of today's training have the courage to filter the abdominal fluid—blood, amniotic fluid, serum—through sterile gauze and administer it intravenously? This has been done with the happy outcome of women living to rear previous offspring.

Such a rigorous training causes one to ponder as to whether or not a physician should be required to engage in a general medical practice for five, possibly more, years before determining upon a specialty. A year, or even two years, of rotating internship followed by a residency in the specialty of his

choice does not mean that he must be, or is, a completed physician. The one who has some years in general practice discovers which particular type of his work is most interesting and in which he is most happy and does best. Then should come his postgraduate study and specialization.

Close observation of interns and residents over the years leads one to suspect that ideals, self-sacrifice, personal and professional honesty, love of the search for knowledge, culture, judgment, common sense, and imagination are qualities rarely sought for in addition to technical efficiency. Rather it seems to be the idea of how soon it will be possible to "pass The Board" and specialize. Can danger lurk in such a situation? May commercialism thrive in such a soil?

In his address at the Twenty-Sixth Annual Meeting of this Association, in 1913, President Miles F. Porter stated, "We are censured by the public as never before and, in a measure, justly so. That we, together with all other professions, trades and callings, should suffer from the epidemic of 'money madness' is but natural and inevitable. But that we should sit supinely, satisfied in our self-righteousness and quietly watch the spread of this scourge, is to be false to ourselves, false to our profession and false to the people." Was he clairvoyant and projecting the shadow of things to come?

One cannot question the outstanding accomplishments of the various specialty boards in elevating the professional qualifications of the physicians desiring recognition as specialists in the various branches of medical practice. May it not be possible that, because of the development of the teaching technique of these branches to meet board requirements, there is grave danger that the Diplomates, especially the younger ones, will lose their sense of proportion in the consideration of the ill individual as a functioning entity, in his own environment, beset by troubles? Because of their superspecialization they may fail in ever being completed physicians.

Specialization is the outcome of the more detailed and more technical development of the practice of medicine. As more knowledge of the various organs of the body has accumulated, it is only natural to expect that the diagnosis and treatment of the diseases of these organs will be undertaken by those physicians who have acquired a special knowledge of them. As a result we find the development of group practice and the establishment of innumerable clinics. It looks strangely as if medicine is endeavoring to follow in the footsteps of large industry in this commercial era and is forming assembly lines, so to speak, in an effort to speed up production. In so doing there is a loss in the perspective of the patient as a person. With the assembled group of diagnoses, often widely divergent, may not the treatment too often be therapy X or Y or Z—possibly XYZ?

The obstetric art is as old as the function of reproduction. Indeed the first case history of medicine is that of an operative delivery under anesthesia. The succinct record of this is found in the twenty-first verse of the second chapter of Genesis.

Of all specialties obstetrics is the most important. In none other is the responsibility for life equal to ours, since with each of our patients at least two,

in Dafoe's experience six, are dependent upon the scientific knowledge and technical skill of the attendant. The obstetrician must be an internist, a surgeon, a pediatrician, a psychosomaticist, as well as an economist, eugenist, and sociologist. In spite of all this, its importance appears to be the least appreciated by recent graduates in medicine, of any of the specialties.

This particular branch seemingly is not appreciated in the curriculum of most schools of medicine. In but a rare few is time for proper teaching allocated to it. One questions if students, or even recent graduates, have a conception of the Ideals, the Responsibilities, the Reward of the Obstetrician.

The obstetrician's ideal of service should be that he may so strive with the talent entrusted to him that the race will be benefited by the assurance of strong and healthy citizens. He must keep before him always that the health of our nation, of all nations, is in great measure dependent upon good obstetrics. It is not possible to develop a strong and sturdy race with physically ill or defective mothers and babies. Without proper care we cannot have other than sickly, defective and injured mothers and infants. Herein lies much of the tragedy following obstetric neglect, the lifelong handicap of mental or physical, possibly both, defectiveness of the offspring and the suffering and inefficiency of the mothers.

Every prospective mother is a challenge to our scientific knowledge and our technical skill. Each is entitled to the best we have within us. After many years and much experience one wonders if even that is good enough and still impatiently rebels against the limitations of his accomplishments which are so far short of the perfection he strives for.

Does not each unborn infant have an inalienable right to demand that it shall be well born? Not by any means is it meant that they shall be ushered into this Vale of Tears with a gold, or even silver, spoon awaiting them, nor even a social security card signed, sealed, and delivered by an all-wise, paternalistic bureau in the National Capitol. But that each shall have a healthy physical body, and that this body shall arrive intact and uninjured in transit. Healthy and happy babies, cared for and reared by mothers who are not mental and physical wrecks as the result of childbearing, will become healthy and happy citizens. Healthy and happy citizens will be sane ones and will not become Communists, Fascists, or Nazis.

Thus the obstetrician of today has responsibility that does not seem to be appreciated by too many of those who render service in this branch of medical care. Nor is this responsibility sufficiently stressed by those entrusted with the teaching of the obstetric art to undergraduates and graduate interns and residents. The obstetric teaching and practice of the present should emphasize the future health of the mother and her infant as well as their immediate safety at the time of delivery.

Recently, at a meeting of an obstetric group, we listened to a presentation dealing with the subject, "Prolonged Labor," in which labors of twenty-four, thirty-six, forty-eight, sixty, even one hundred and twenty hours were discussed. One who had spent seven years in psychiatry where an opportunity was afforded

to secure an extensive experience with idiocy, imbecility, and other types of mental aberration could not but speculate as to the effect of such an ordeal. May one not be permitted to question as to whether or not it is such an outstanding obstetric accomplishment to deliver vaginally a living child with the mother being fortunate enough to live through an experience of this character. In the light of experience it seems more than plausible that many of the mental, moral, and even criminal misfits of the populace may be such as the result of microscopic cerebral injury due to anoxia, minute hemorrhages in the brain tissues, et cetera. May not much of our crime, mental obliquity, and disease be dependent upon birth traumas for their basic etiology?

Experience has abundantly proved that intelligent prenatal supervision of the pregnant woman pays a tremendous dividend upon the investment of the obstetrician's time, in the lowering of maternal mortality from toxemia, infections, blood dyscrasias, and malnutrition due to disturbances of metabolism, and so on. Equally great is our responsibility in lowering the maternal morbidity of abortions, miscarriages, the prevention of difficult or impossible labors, when we give conscientious prenatal study and care to our prospective mothers.

In the same connection we must bear in mind that we have a responsibility for the high neonatal death rate of infants. Many of these are due to etiological factors which are present practically from conception. Indeed, some may exist even before conception occurs. If these infants are to receive the greatest benefits from our present-day knowledge, we must begin our care of them nine months before their birth.

Since each of us is from practical experience so cognizant that early and conscientiously given scientific care reduces the catastrophes of pregnancy for both mother and infant, are we as teachers of undergraduates, interns, residents, and postgraduate students meeting our own responsibilities as instructors? It might be well to ponder the thought.

But let us not neglect likewise to impart to those who may come under our teaching care that, even though the specialty of obstetrics is so time-consuming and arduous, yet no service in all of medicine gives such a sense of satisfaction to the physician as is the reward of the obstetrician when he feels that without his care either the mother or child, or both, would have perished.

Permit me, in closing, to reiterate my plea for the better orientation of the medical student about the patient, what he is, how he functions, how he feels and thinks and acts in his own environment. This orientation should take place as the student travels through his medical school years, in order that he may and will understand the individual as a whole and understand also what he himself is endeavoring, as a physician, to accomplish.

CARCINOMA OF THE CERVIX ASSOCIATED WITH PREGNANCY*

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THE rarity of the lesion in no way lessens the responsibility for early diagnosis and the institution of adequate treatment. The diagnosis of carcinoma of the cervix associated with pregnancy should present few difficulties, if the possibility of its existence is admitted.

The diagnostic signs of carcinoma of the cervix during pregnancy are the same as the signs of the lesion in the nonpregnant cervix. Abnormal discharge or bleeding that is painless, irregular, progressive in amount, and prone to follow traumas warrants a diagnosis to be confirmed by a biopsy and a pathological report.

Bleeding late in pregnancy must be investigated in an effort to rule out placenta previa, or abruptio placentae. Accurate pathological diagnosis of the tissues removed cannot be overemphasized, for microscopic variations and changes in the pregnant cervix are not too well known, and may, if not thoroughly understood, be confused with malignancy or suggest malignant changes, and lead to unnecessary and radical treatment. Benign lesions should not be treated during pregnancy, but should be carefully watched, and frequent cytological studies or biopsies should be carried out if the diagnosis is questionable. Treatment should be withheld until the diagnosis has been confirmed. The patient should not be subjected to extensive irradiation therapy which may not only deform or destroy the fetus, but also may produce deformity and permanent injuries to the mother.

The practice of cervical visualization and biopsy of all abnormal lesions should always be carried out, and when properly done need not cause abortions or excessive bleeding. Early diagnosis will not be made until women abandon procrastination and superstitions and learn to face facts, and until the doctors become ever zealous in the search for the causes of abnormal bleeding and discharge from the vagina.

The now average presence of nine months' lapse between the appearance of the symptoms and institution of treatment of the lesion is in a great part due to the two factors mentioned above: the patient's neglect and the doctor's delay in finding the cause.

There are at least three schools of thought regarding the influence of pregnancy on carcinoma of the cervix:

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TABLE I. TUBAL PREGNANCY AND ABORTIONS, FIRST TRIMESTER

PATIENT	AGE (YEARS)	RACE	PARITY	DURATION OF PREGNANCY	FATE OF PREGNANCY	PATHOLOGIC REPORT OF CERVIX	TREATMENT	RESULTS
E. D. Case 1	34	Negro	Para iv Gravida v	Ectopic pregnancy 8 weeks	Operated upon	Squamous-cell Ca., Grade I	Supracervical hysterectomy; bilateral salpingo-oophorectomy 2,900 mg. hr. radium	Well 16 years after
G. H. Case 3	26	White	Para i Gravida vii	5 weeks	Incomplete abortion D. and C.	Squamous-cell Ca., Grade iv	Refused treatment	Moved after 1 year; no follow-up
A. B. Case 6	34	White	Para ix Gravida xiv	18 weeks	Incomplete abortion	Squamous-cell Ca., Grade III	1,950 mg. hr. radium 6,000 r. x-ray supracervical hysterectomy 3,500 mg. hr. radium 6,400 r. x-ray	Died after 26 months
R. G. Case 7	33	White	Para ii Gravida v	12 weeks	Criminal abortion D. and C.	Squamous-cell Ca., Grade II	2,800 r. x-ray Wertheim operation with radical iliac dissection	Living and well 5 years
E. S. Case 8	43	White	Para vii Gravida xi	9 weeks	Incomplete abortion	Squamous-cell Ca., Grade II	D. and C.; 5,600 r. x-ray; bilateral salpingo-oophorectomy, iliac dissection. 11,200 r. x-ray 8,400 mg. hr. radium	Living and well 5 years

1. Peller, as quoted by Baer,[1] after demonstrating that the relative number of carcinomas occurring during pregnancy was significantly less than the number occurring in similar age groups in nonpregnant women, concluded that pregnancy not only increases the resistance to cancer, but raises the average age of its occurrence and retards its progress.

2. Emge[2] concluded from his experimental animals that the role of estrogenic hormones in the production of cancer is secondary to and limited by the hereditary factors.

3. There are others who believe that pregnancy and the associated high estrogen levels influence the rate of growth and rapidity of spread of the carcinoma. These findings we believe are consistent with the clinical progress of the disease when associated with pregnancy.

An examination of eighteen reports from the literature on the incidence of carcinoma of the cervix associated with pregnancy gives an average of 0.056 per cent. This low figure is not out of line when we consider that the highest incidence for carcinoma of the cervix is beyond the child-bearing age. With the present stress laid on prenatal care, carcinoma of the cervix should be diagnosed earlier when associated with pregnancy, and expecially in the first two months when painless, irregular bleeding (80 per cent) and an abnormal discharge (20 per cent) should be thoroughly investigated.

Material

During the past fifteen years, 1933 to 1948, there were 29,394 obstetrical patients admitted to the Louisville General Hospital. During this same period of time, there were twelve cases of carcinoma of the cervix associated with pregnancy that were confirmed by pathological diagnosis. This is an incidence of 0.04 per cent or about four cases per 10,000 obstetrical cases. The twelve cases represent 1.54 per cent of all the cases of carcinoma of the cervix treated in the Louisville General Hospital during this fifteen-year period.

The average age of the patients was 29 years (16 to 43 years), or fourteen years less than the average age of the nonpregnant woman with carcinoma of the cervix. Seventy-five per cent were between 30 and 40 years. The average parity was four (three to eleven). Three of the women were Negroes.

Clinically, the carcinomas of the cervix were classified according to the League of Nations Classification:

Group I:	4 cases
Group II:	2 cases
Group III:	2 cases
Group IV:	4 cases

Pathologically, the cervical lesions were all squamous-cell carcinomas and corresponded in their pathological grading closely to the clinical grouping.

Regardless of the method of classification, over one-half of the patients when first seen were hopeless as regards the possibility of cure. One patient came in after being in labor for some hours and did not have excessive bleeding; another, after delivery in the home, for excessive bleeding.

The diagnosis of carcinoma of the cervix was made in six of these patients before the period of viability of the fetus. This fact suggests that the carcinoma of the cervix existed previous to the inception of the pregnancy. It is believed by some authors that the presence of carcinoma prohibits conception.

All of the patients were in the first trimester of the pregnancy. One had carcinoma associated with ectopic pregnancy, and after operation and radium has been well for sixteen years. The other four cases were associated with abor-

TABLE II. PREGNANCIES AT TERM OR POST PARTUM

PATIENT	AGE (YEARS)	RACE	PARITY	DURATION OF PREGNANCY	FATE OF PREGNANCY	PATHOLOGIC REPORT OF CERVIX	TREATMENT	RESULTS
C. T. Case 4	36	White	Para vii Gravida x	38 weeks	Living child	Squamous cell Ca., Advanced Grade IV	First seen in labor, refused treatment. 2 months later had 4,800 r. x-ray 2,200 mg. hr. radium	Died 6½ months
A. H. Case 5	32	White	Para vi Gravida vii	28 weeks	Living child	Squamous cell Ca., Grade IV	Poro section 1,200 r. x-ray 8,800 mg. hr. radium	Died 8½ months
E. R. Case 9	29	White	Twins Para v Gravida iv	40 weeks	Living child	Squamous cell Ca., Grade IV	5,600 r. x-ray bilateral salpingo-oophorectomy, iliac lymphadenectomy 5,000 mg. hr. radium 500 r. x-ray	Died in fourth year
M. W. Case 10	36	Negro	Para iv Gravida iv	40 weeks	Living child	Path. diagnosis only—squamous-cell Ca., Grade I	Poro section Total hysterectomy No radium	Living and well 2½ years
D. C. Case 12	34	White	Para viii Gravida ix	Term	Living child	Squamous cell Ca., Grade III, Stage I	5,700 mg. hr. radium Excision; Wertheim hysterectomy	Died 4 years later

TABLE III. CARCINOMA IN SITU

PATIENT	AGE (YEARS)	RACE	PARITY	DURATION OF PREGNANCY	FATE OF PREGNANCY	PATHOLOGIC REPORT	TREATMENT	RESULTS
C. T. Case 2 1931	16	Negro	Para i Gravida ii	Term 40 weeks	Classical section, living child	Squamous cell Ca., Grade I	Cauterization of lesion. Has had subsequent pregnancy and no recurrence	Living and well 15 years
G. M. Case 11 1948	28	Negro	Para 0 Gravida i	Near term	Spontaneous delivery, living child	Squamous-cell Ca., Grade I	Cauterization of lesion. No recurrence. Being carefully followed. Now pregnant	Living and well 1 year

tions; one patient refused treatment and follow-up could not be made as the patient moved. One (Stage III), in spite of improvement under radium, x-ray, operation, and additional radium and x-ray, died in two years.

Two other patients, Stage II, after radium and x-ray therapy and operation (Wertheim), are living and well five years after treatment.

Although there were delivered six living children from this group, one was a premature (3 pounds, 8½ ounces) infant who died on the second postpartum day. The remaining five infants are alive and well to date. There is only one mother living 2½ years after operation. This case was not clinically diagnosed as carcinoma of the cervix before operation and was found only on pathological diagnosis to be Stage I, Group I, carcinoma of the cervix. Although she is alive and well, and no radium or x-rays were given, we can count this as a Stage I surgical cure.

The duration of the remaining pregnancies ranged from twenty-eight weeks to full-term pregnancy. All of these cases were seen for the first time after the child was viable and treatment instituted immediately, except that two patients refused treatment.

In the years 1933 to 1938, we endeavored, when possible, after emptying the uterus in the Stage II or more extensive cases, to do a supracervical hysterectomy and bilateral salpingo-oophorectomy to block off the extension of the growth and possible infection, and then follow with 4,500 to 8,000 mg. hr. of radium into the cervix and on each side of the cervix, then give 6,000 to 8,000 r of x-ray therapy through four or five different portals, using the cervix as a point of focus for treatment. This, we now feel, was not completely satisfactory, and we have adopted a more radical attitude.

Results

The question of treatment of carcinoma of the cervix was for many years apparently settled in favor of radiation therapy alone, but now that a plateau of results with this form of treatment has been reached, showing at best less than 50 per cent five-year arrests, we feel that further consideration should be given, and an outline of treatment is being reopened in favor of a combination of radium, x-ray, and radical surgical removal in Stage I and Stage II cases, and the reports are more gratifying.

In this series of twelve cases there were six with radical operation, two cases of Stage III or IV that responded most satisfactorily to x-rays and radium therapy, but these two patients later were operated upon and died in the fourth postoperative year from generalized carcinoma metastases. These cases were too far advanced in the beginning to permit a five-year arrest but the patients were made quite comfortable for years and would, no doubt, have died sooner had they not been treated.

In two cases, Stage I, with radium and Wertheim operation with iliac dissection, the patients are living and well over five years after operation.

In two cases, Stage II, with radium, x-ray and Wertheim operation, the patients are living and well over five years later.

In this series, there was no operative mortality. In the series studied there were five living children and six living patients, five over five years, or a 50 per cent salvage.

We know that twelve cases are far too few to draw conclusions from, but from study of the literature on the subject and from our own experience, we feel that the treatment of carcinoma of the cervix associated with pregnancy, when the diagnosis has been definitely confirmed, must be divided into at least three plans:

1. Destroy the lesion. (This is the most imperative.)

A. Empty the uterus by hysterotomy and do not curette the lesion.

B. Insert radium into the uterus and on either side of the cervix to over 4,500 to 5,000 mg. hr. in one to three applications.

C. Follow by deep x-ray therapy, when indicated by possible metastasis, by accepted techniques through from four to six portals, usually a total of 4,000 to 6,000 r, dependent upon the tolerance of the patient.

D. Six weeks to three months later, institute radical resection of the uterus, tubes, ovaries, and pelvic and iliac glands (Wertheim type) when the patient's general condition warrants the operation in the judgment of the surgeon.

2. Only in the very exceptional condition should the life of the mother be jeopardized to save the child. If so indicated, start treatment with radium to the lesion, await viability, then deliver the child, preferably by Porro section, and follow by deep x-ray therapy and radium to the local lesion. With this type of treatment, 20 per cent of the cases result in deformed children and the end results in the mother are worse.

3. Save the child and give palliative therapy to the mother in the late cases after viability, where the cure of the mother from the beginning has a hopeless outlook.

A. We feel that abdominal delivery is the method of choice. It prevents hemorrhage, lessens infection, extension of growth, and subinvolution. Porro section is usually advocated in these cases.

B. Extensive radium and x-ray therapy as indicated and as tolerated, carefully checked by cytological studies and biopsies to determine the response to x-ray and radium therapy.

C. Careful follow-up of progress of x-ray and radium treatment. (Space and time do not permit a detailed discussion of techniques and application of doses used, as these have been developed to an acceptable point.)

D. Radical surgery, if possible, after thorough treatment by radium and x-ray has been carried out and the improvement has been greater than anticipated and the possibility of iliac node involvement is definitely present. By removal of these distant metastases we can salvage some of these patients and extend the time of arrest in such cases.

During this process of irradiation the response of the growth should be carefully studied by Papanicolaou stain and biopsies to see if the desired response is being obtained, and if this is not satisfactory, surgical removal should be instituted when feasible, for in these radium-resistant cases the possible surgical operability may be jeopardized by waiting until completion of the therapy and possible cures may be sacrificed.

Abdominal delivery, we believe. is definitely indicated in all cases more advanced than Stage I, whether it be to remove a missed abortion or to induce abortion or to procure a live child. We feel that the products of conception should not be allowed to be delivered spontaneously because of possible hemorrhage, spread of carcinoma, and/or resulting subinvolution and infection. Penicillin and antibiotics should be used prophylactically and postoperatively but must not be used to supplant proper judgment and good surgical technique in the handling of these cases.

The fetal prognosis depends, of course, primarily on the stage of the pregnancy at the time the carcinoma is discovered and treatment started. Irradiation or surgical interruption before the viability must of necessity sacrifice the infant, and we advocate that the infant mortality in these cases not be considered. After viability, the plan of treatment may be that method which may save the child, provided that it does not decrease the chances of cure in the mother. We do not believe in temporary delay in treatment to get a viable child, for twenty per cent of these children are deformed at birth as result of radiation therapy.

If the carcinoma is found at term, and the mother's condition is hopeless, first consideration should be given to the life of the child, and only palliative irradiation therapy to the mother carried out.

Fig. 1.—Carcinoma in situ. Patient well after sixteen years. No treatment.

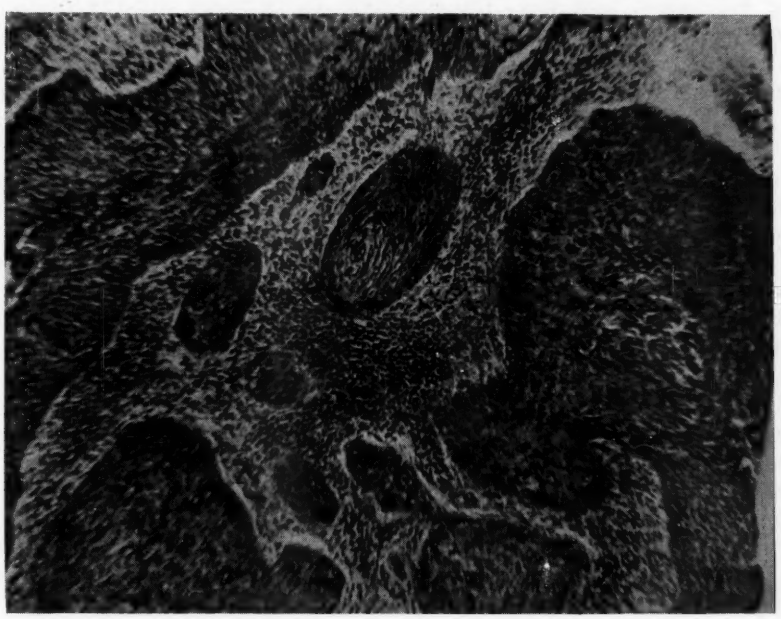

Fig. 2.—Extensive carcinoma of cervix with pregnancy at term.

We feel that in cases of early carcinoma of the cervix, Stage I and Stage II, associated with pregnancy, with the resulting stimulation from the effects of pregnancy, it is more imperative that radium and x-ray be given as indicated and

followed by radical surgery and gland resection. In this series, our use of Wertheim and iliac dissection have given the most satisfactory results.

As has been previously reported, 16 per cent of the cases of carcinoma of the cervix recur in the local or original site of the growth, and 32 per cent of cases operated upon by Wertheim and iliac gland dissection have glandular metastasis after complete x-ray and radium therapy has been carried out. It is from this group that we hope to extend our cures with radical surgery when possible.

In the two cases of carcinoma in situ, or intraepithelial cancer, or early Stage I, no radiation therapy was given, or operation advised, and the patients have had repeated pregnancies without recurrences and are alive and well from two to sixteen years later. These Stage I cases should be considered strictly as histological and clinical and should be regarded as indicating one of three clinical possibilities: (1) that the biopsy has been taken from the periphery of an advanced cervical cancer, (2) that microscopic invasive cancer is present elsewhere in the cervix, or (3) that only carcinoma in situ is present and no invasion has yet taken place.

Therefore, each case should be evaluated clinically, the gross appearance and feeling of the cervix studied by the same person. If biopsy shows only carcinoma in situ, but the gross appearance of the cervix is suspicious of more advanced cancer, additional biopsies or conization of the cervix should be carried out to determine the extent of the lesion; then the case should be followed carefully, with frequent Papanicolaou stains and/or biopsies to determine any evidence of malignant change.

Novak[3] believes that noninvasive cervical cancer is the beginning of infiltrating cancer and may be of extremely variable duration.

Pund and associates[4, 5, 6] find that 4 per cent of all discovered cervical carcinomas are early preinvasive, the average duration of preinvasive cervical cancer being 6.5 years, and that the majority of cervical cancers become obvious eleven years after incipiency, or five years after invasion.

McIlrath and Hellestrand[7] state that chronologically, microscopic changes in the pregnant cervix were found to be thickening of the squamous epithelium, decidual changes in the stroma as early as ten weeks, increased size and number of glands at four to five months, plus secretion and slight hyperplasia of the cells, vascularity and edema of the stroma by five to six months, and stroma decrease with squamous epithelial thinning and replacement of stroma by glands by six to seven months. Metaplasia was marked in one-half of cases, and most of the mucosa shed at birth was regenerated by the seventh to fourteenth postpartum day.

Fluhmann[8] describes adenomatous proliferation of the cervical glands as a characteristic finding in thirty-two cervical lesions, and less frequently papillary outgrowth, inflammation, epidermization, and hyperactivity of the basal-cell layers of the squamous epithelium simulating malignancy, and decidual reaction.

Murphy and Herbert[9] found that among biposies from fifty cervices of pregnant women thickening of the superficial squamous layer was found in all cases, inflammation in 64 per cent (three times more often at the squamocolumnar junction in multiparas than in nulliparas), decidual formation in 22 per cent, epidermization in 18 per cent, and increased basal-layer activity in 6 per cent. There were no complications resulting from these biopsies, bleeding being controlled by cotton packs.

We believe that early cancer of the cervix is more frequent than has been recorded and a clear understanding of the treatment of carcinoma in situ is needed so as to define our responsibility to these patients.

In the two cases of carcinoma in situ (intraepithelial cancer), early Stage I, we are still at a loss as to treatment. With the various types of treatment, the

curability rate has been high but the ultimate fate of these patients who have not been treated, or who have failed to be cured in spite of treatment, reveals that some have had repeated recurrence after five years following hysterectomy. So we are still at a loss as to the limits of our responsibility in these cases.

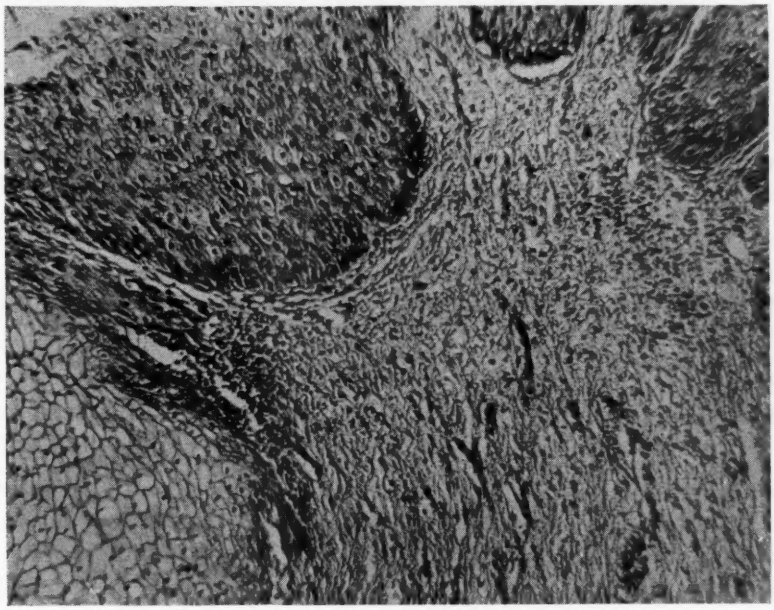

Fig. 3.—Carcinoma in situ. Patient well for two years.

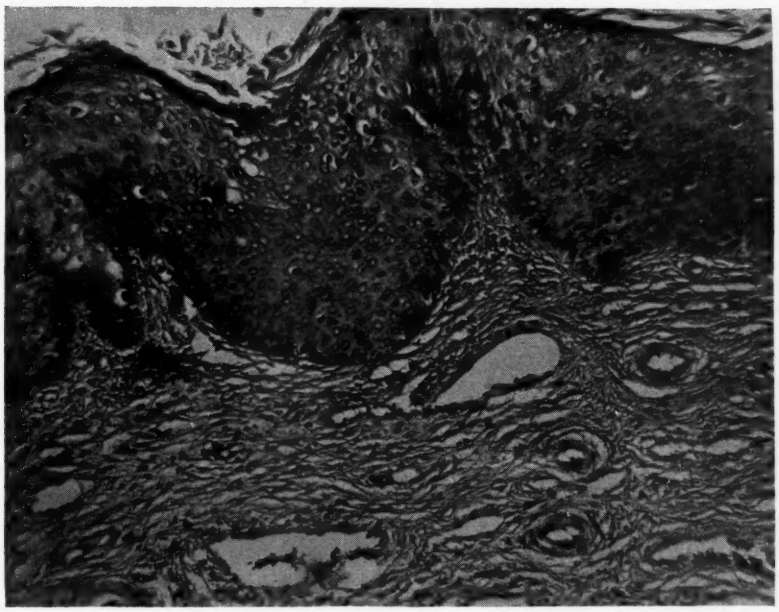

Fig. 4.—Carcinoma in situ.

We feel that in these early lesions which are confined to the cervix (carcinoma in situ), the combination of curative doses of radium followed by wide excision, as advocated by Te Linde,[10] is likely to be the best solution. These pro-

cedures were not done in our two early cases because of the controversy up to that time over the subject. Both women have been carefully watched and both have had subsequent pregnancies without any suggestion of recurrence of the lesion or any subjective symptoms. What remains in store for them five years from now? We shall watch for and be ready to care for it when it arises.

Summary and Conclusions

1. Study of twelve cases of carcinoma of the cervix associated with pregnancy has been presented, with an urgent recommendation of prompt and thorough investigation of bleeding during pregnancy and inspection of the cervix and biopsy of all definite lesions.

2. Lesions should be diagnosed earlier and treatment instituted immediately to give cures to the mothers.

3. More comprehensive knowledge of the cervix in the first, second, and third trimesters should prevail to avoid overzealous treatment, and permit a concise and definite treatment of the early cancerous lesions.

4. High fetal mortality is inevitable and should be considered only if the lesion is too far advanced to save the mother and the child can be saved.

5. All products of conception should be removed by the abdominal route. No patient should be allowed to deliver spontaneously because of the dangers of hemorrhage, infection, and dissemination of the malignancy.

6. In the selected cases, we feel at present that the best results are obtained by combination of radium, x-ray, and radical surgery.

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Discussion

DR. R. D. MUSSEY, Rochester, Minn.—The authors have properly called attention to the necessity for constant vigilance during the period of prenatal care in order that unusual complications, such as carcinoma of the cervix, may not be overlooked.

Maino and I* reported in 1944 that pregnancy complicating carcinoma of the cervix occurred among 0.7 per cent of the patients with carcinoma of the cervix observed at the Mayo Clinic between July 1, 1909, and Feb. 1, 1940; during this period twenty-five cases of carcinoma of the cervix and one case of sarcoma of the cervix were recorded as occurring coincidentally with pregnancy. Almost all of the patients consulted us because of the lesion of the cervix; some came soon after termination of pregnancy.

Recently Foust and I examined the data relating to the coincidence of carcinoma of the cervix and pregnancy as observed by us since those cases previously reported. We have

*Am. J. Obst. & Gynec. **47**: 299, 1944.

summarized the data concerning those patients observed in the same period of time as those reported by the essayists: namely, between Jan. 1, 1934, and Dec. 31, 1948, inclusive.

Data were obtained from the records of 15 patients, including 7 patients previously reported on and 8 observed since Feb. 1, 1940. Four of the 15 patients are known to have died, 9 are known to be alive, 2 have not been heard from currently, although they are known to have been alive seven and five years, respectively, since their carcinomas were treated.

In addition to the value of early diagnosis of carcinoma of the cervix, treatment is of paramount importance.

Of the 15 patients I have mentioned, 7 underwent complete abdominal hysterectomy, usually of the Wertheim type; 2 underwent vaginal hysterectomy; 4 of the foregoing were treated with radium and roentgen rays; and 4 others not operated on also received radium and roentgen rays. One patient who had undergone abdominal cesarean section and supravaginal hysterectomy for an advanced lesion was given palliative irradiation. The condition of one patient, gravida vi, para iii, 35 years old, who was examined on March 14, 1944, two weeks after delivery, with a cauliflower tumor of the cervix (squamous-cell epithelioma, Grade II, Stage II), is of unusual interest. She received a total of 7,265 mg. hr. of radium therapy in and around the cervix. Shortly after the last application of radium, laparotomy and dissection of the pelvic glands (Taussig) were done. Both the right and left obturator lymph nodes were found to be involved with carcinoma, and were excised. Bilateral salpingo-oophorectomy was done; the uterus was not removed. Four months later biopsy of a specimen from the cervix again disclosed squamous-cell epithelioma, and 800 mg. hr. of radium were applied to the cervix. This was followed by a course of roentgen-ray irradiation for four days, which was repeated six months later. At examination in July, 1949, this patient was found to be in good health and without evidence of recurrence.

Evidence indicates that among well-nourished women who are pregnant the rate of growth of carcinoma of the cervix is accelerated. In the group of 26 patients with malignant disease of the cervix previously reported on, all who completed the usual duration of gestation were dead within two years, whether or not the birth occurred through the birth canal or by abdominal section. Among the last 8 patients observed by us since the foregoing report, 3 were delivered at term through the cervix, 1 of whom is living five years, 1 four years, and 1 three years after treatment, respectively, with (1) radium and Taussig's operation, (2) radium and roentgen rays solely, and (3) total abdominal hysterectomy for epithelioma in situ discovered and established by biopsy at examination six weeks post partum.

Carcinoma in situ was discovered in another case in December, 1948, at the time of curettage for incomplete abortion at ten weeks' gestation. This was treated by vaginal hysterectomy, and there has been no recurrence at the time of examination four months later.

We agree with the admonition of the essayists that abnormal vaginal bleeding in the course of pregnancy should be carefully investigated.

We feel that the methods of treatment must be varied, depending on the stage of the carcinoma of the cervix, the duration of gestation, and the physical condition of the patient.

If the extent of the lesion will permit operation and the fetus is not yet viable, total abdominal hysterectomy (Wertheim) is followed by irradiation. Carcinoma of the cervix in situ appears to justify vaginal or total abdominal hysterectomy without extensive dissection of glands and irradiation. If the lesion is operable and the fetus is viable, cesarean section is followed by panhysterectomy, dissection of pelvic lymph nodes, and postoperative irradiation.

In cases in which the lesion is inoperable and the fetus is viable, cesarean section is followed by irradiation. In cases in which the lesion is not operable and the fetus is not yet viable, irradiation is employed; this is followed by death of the fetus and abortion. We do not advise hysterotomy unless the fetus is viable. Occasionally, a lesion which is seemingly inoperable or at best borderline may be treated by irradiation followed by laparotomy and dissection of the pelvic glands.

DR. ROBERT L. FAULKNER, Cleveland, Ohio.—The clinical diagnosis of lesions of the uterine cervix during pregnancy presents problems somewhat different from those of the ordinary cervix. In the first place, bleeding granular areas may turn out to be nothing more or less than decidual reactions. In the second place, excess edema natural to pregnancy frequently exaggerates the gross appearance of any papillary erosion. As a result, in clinical diagnosis of lesions during pregnancy, "many are called but few are chosen," or, in other words, biopsies are, or should be, made of many cervices, though relatively few turn out to be carcinoma.

Aside from the decidual reactions in the cervix associated with pregnancy, histological diagnosis varies from the usual in that there is "more of everything" than in the nonpregnant organ. Extensive squamous metaplasia is frequent. Glandular epithelium is hyperplastic, hence the common expression of adenomatous proliferation. The mucous epithelium is hypersecretory. In addition to squamous metaplasia, squamous epithelium is frequently thick and acanthotic with the associated activity of the basal layer common to acanthosis. The significance of these changes in squamous epithelium has not yet been entirely settled, but there is the thought that changes of this kind may exist in the cervix of pregnancy and be hormonal in origin rather than denote dangerous epithelial activity. This has a bearing on the diagnosis of so-called carcinoma in situ.

Actual carcinoma when present in the cervix of the pregnant uterus is just as easy to establish diagnostically as at any other time. Nine patients in our clinic have had frank carcinoma associated with pregnancy, out of 1,233 cervical carcinomas, or 0.73 per cent of all carcinomas treated. There is no way of telling how many obstetrical patients were represented by these nine patients since they were probably only part of the actual carcinomas from two different institutions. All of these discovered during the course of pregnancy were treated by abdominal hysterotomy, x-ray, and radium. Of the nine, two survived five years. One has survived fourteen years.

None had the extensive treatment outlined by the author. Although it is well known that the lower abdomen tolerates insult well, it seems that there should be a limit to what tissues anywhere will stand. Hysterotomy, x-radiation, radium therapy, and finally radical operation seem like quite a chain of events, all to take place in the limited area of the pelvis. I would like to know more of general tissue healing and fistulas resulting. Even in hysterectomies following lesser radiation for carcinoma of the endometrium, it is my impression that about one out of three has late interference with wound healing, evidenced by vaginal vault slough, pelvic infection, or some other trouble not accompanying hysterectomy without radiation preceding the operation.

DR. HERBERT E. SCHMITZ, Chicago, Ill.—I would like to urge a little more careful use of the terms employed in the classification of carcinoma. The authors report Groups I, II, III and IV in certain instances and Dr. Johnson tells us that this is the League of Nations' Classification. I believe that the League of Nations use the word "Stage" not Group, Group I, etc., in the Schmitz classification. During the discussion of treatment of cases, both stage and grade are used, which is confusing. There is one patient with Stage IV carcinoma of the cervix, or Grade IV, and I do not know whether it is microscopic grading or clinical classification, who lived more than one year without treatment. In all probability there was a good deal of edema and inflammation caused by the pregnancy associated with this carcinoma, otherwise a Grade IV or Stage IV patient would not have lived that length of time without therapy.

I would furthermore like to add my thanks for the abandoning of the supravaginal operation, or the so-called "Porro" section in carcinoma of the cervix, which has been utilized so frequently in the past. This procedure leaves a stump after the lymphatic drainage has been interfered with and this makes treatment most difficult.

DR. EMIL NOVAK, Baltimore, Md.—I should like to comment on one point, of pathologic rather than clinical interest, as regards cases of carcinoma in situ observed in pregnancy. The whole question of intraepithelial carcinoma is still a somewhat confused one, and we still know comparatively little as to the chronological and sequential relation

between this lesion and actual invasive cancer. When one considers the changes produced by estrogen in the vaginal mucosa, it is not surprising that the far greater and more prolonged hormonal excess characterizing pregnancy may bring about profound changes in the cervical mucosa. We know a good deal about cyclical and pregnancy changes in the endocervical epithelium, thanks chiefly to the studies of Sjövall and Stieve. But there has been almost no direct study of the cervical squamous epithelium, though one might expect that its hormonal responsiveness would be similar to that of the vaginal epithelium. We are at present studying this problem from material collected by surface biopsies of the cervix, but cannot as yet present any conclusions on the subject.

Hellman and Epperson have been making routine cervical biopsies of pregnant women in the Department of Obstetrics at the Johns Hopkins Hospital, the biopsies being done at the twelfth week of pregnancy, intra partum, and at various periods post partum, and I have had the opportunity of seeing some of their microscopic sections. Already they have encountered a considerable group of cases in which the stratified squamous epithelium of the pregnant cervix has shown marked cell overactivity, in some corresponding to the picture of intraepithelial carcinoma. Moreover, in many of these cases, follow-up biopsies made at various stages after delivery have shown complete disappearance of the lesion. This suggests that the cell changes of intraepithelial carcinoma may at times be completely reversible, certainly in pregnancy and probably also in the nonpregnant woman. This still further confuses the significance of this much discussed lesion, and about all that we can at present say is that preinvasive cancer may, or may not, in an indeterminate number of cases, at some unpredictable time in the future, be followed by the development of genuinely invasive cancer.

Dr. JOHNSON (Closing).—In answer to Dr. Mussey, we find about 16 per cent of the cases of carcinoma of the cervix have recurrence locally, and about 30 per cent of the cases that have been thoroughly treated with x-ray and radium have evidence of metastases in the pelvic glands. It is in this type of case that, depending on the physical condition, we advocate a Wertheim resection. If you wait too long after treatment with radium and x-ray three months or more, you will not be able to dissect out the area.

In answer to Dr. Faulkner, we have not as yet had any fistulas. We do have about 15 per cent with bladder symptoms for a period of six weeks to six months, a condition which is very disturbing to the individual. However, I feel that, if the Wertheim is associated with some bladder disturbance, the dissection has been more complete, therefore more cancer-involved tissue is removed that has not been reached by irradiation.

Dr. Schmitz' correction of the classification is correct. It should be Stage and not Group.

In answer to Dr. Kennedy's question, the two cases of carcinoma in situ were first seen in their first pregnancy. There were no lesions except a well-localized lesion about the size of a large pea, and this was excised and cauterized and those patients have had no recurrence with subsequent pregnancies. I would say that four out of the twelve patients had what you might call a "clean cervix" when first seen.

It has been very interesting to hear from Dr. Randall of the 100 pregnant patients with carcinoma delivered spontaneously without any hemorrhage. We have had two cases, and one did not have very much hemorrhage. The other patient came in post partum and had to have repeated transfusions.

We have had cases that did not respond to x-ray and radium therapy, and have found later we have allowed them to go beyond the stage where we could cure the patient either by x-ray or radium or surgery. It is constant vigilance and study of these cases that will permit us to salvage more in this group.

PELVIC TUMORS COMPLICATING PREGNANCY*

CARL HENRY DAVIS, M.D., COCONUT GROVE, FLA.

THERE are many reports on pelvic tumors complicating pregnancy. It is evident that any tumor which does not prevent a pregnancy may at some time be present in a pregnant woman and serve as a more or less serious complication. Not only intraperitoneal tumors but also the more rare extraperitoneal tumors may be found. Fortunately, most of our problems with pelvic tumors complicating pregnancy arise from cysts and fibroids. Those in my experience have all been from these and this discussion will be limited to brief reports of a few personal cases.

Fibroids constitute the less serious group in that they rarely necessitate an emergency operation during pregnancy, although red degeneration may present a diagnostic problem and many observers believe that fibroids increase the incidence of abortion. Three typical cases are presented:

CASE 1.—Mrs. Y. was known to have a pedunculated fibroid the size of a tennis ball attached to the left side of the fundus of the uterus, prior to her pregnancy. As there had been no discomfort associated with the tumor and its location was such that no difficulty would be expected during labor, she was advised to try to get pregnant. However, when she was in the sixth month she developed acute left-sided pain, and torsion of the tumor was the tentative diagnosis. After observation for two days it was evident that surgery was indicated and at operation it was found that two turns of the tumor had completely shut off its blood supply. Convalescence after myomectomy was uneventful, and she delivered normally at term.

CASE 2.—My laboratory technician informed me one afternoon that I should begin to look for someone to take her place as she was about three months pregnant. She had never had a pelvic examination although she had been married for two years. Examination showed that the uterus was the size of a three-month pregnancy and that it was elevated by a very hard tumor large enough to fill most of the pelvis. The tumor was easily movable and was diagnosed as a pedunculated fibroid of the uterus. This tumor was attached just above the cervix and would have blocked the pelvic canal at term had it remained. It was removed through a Pfannenstiel incision and she delivered normally at term.

CASE 3.—Mrs. J. H., aged 35 years, gave a history of two earlier pregnancies which terminated at six weeks and at two and one-half months. For a third time she became pregnant and on examination it was found that she had a rather large solid tumor that filled most of the pelvis and elevated the uterus high up in the abdomen. This tumor seemed to be fixed and it was believed to be one that had grown into the broad ligaments. Obviously, this was not the type of tumor where removal during pregnancy should be considered. Fortunately, she was able to carry this pregnancy and late in the ninth month a cesarean section was performed. I had hoped that it would be possible to remove the

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tumor and save the uterus, but a hysterectomy was necessary. From the pictures made during the operation it is evident that any attempt to remove the tumor during pregnancy would have resulted in a loss of the pregnancy.

If a woman who has fibroids becomes pregnant she has an excellent chance to complete the pregnancy without need for surgery and without undue risk to herself. On several occasions I have had to remove a pedunculated fibroid during pregnancy because of torsion, but in no instance was the operation followed by loss of the pregnancy. In case an operation during pregnancy is indicated, the Pfannenstiel incision is preferred because it leaves a strong abdominal wall. In the older age group with fibroids, cesarean section at term may be indicated and I have had a number of patients in whom cesarean section was followed by multiple myomectomy. I have also had a fair number of patients with fibroids, delivered through the natural passages, on whom it was necessary to do surgery during the postpartum period because of degenerative processes in one or more of the tumors.

Cysts present more serious problems when they complicate pregnancy owing to the ever-present threat of torsion. The following case illustrates some of the difficulties which may arise from a mistake in diagnosis when a cyst is not recognized.

CASE 4.—Mrs. M. N., aged 23 years, was married in August, 1927. When I first examined her on Feb. 20, 1928, it was my impression that she was at least four months pregnant although she reported that her last period started Dec. 11, 1927. On April 4, 1928, she developed a severe right-sided pain and was sent to the hospital for observation. The white blood count was 13,900 and the urine showed a considerable number of pus cells. The urologic consultant was certain that she had an acute pyelitis even though her temperature was only slightly elevated. He advised ureteral catheterization which was done with some temporary relief. But her general condition gradually deteriorated and after further consultation, on April 27, a vaginal hysterotomy was performed and a fetus of about 4½ months was delivered. Although the mass remained large, she improved and was discharged from the hospital. On May 15, 1928, her mother reported that her daughter had very severe pain and had been unable to retain fluid or food since the previous day. She was promptly returned to the hospital by ambulance. Examination revealed that she had an abdominal mass that reached the navel, and a doughy mass was palpated in the cul-de-sac. It was evident that she had an acute abdominal condition with intestinal obstruction. She was taken to the operating room as soon as possible for exploratory operation. None of us who had seen her appreciated thus far our original mistakes in diagnosis. When the abdomen was opened, it was found that she had a gangrenous ovarian cyst that measured 16 by 12 cm. There were three or more twists of the pedicle. A gangrenous appendix was adherent to the cyst. These were removed. Then on exploration of the cul-de-sac to determine the reason for my impression of a doughy mass, a gangrenous loop of ileum was brought into view. A piece of intestine 25 cm. long was resected. Fortunately, the postoperative course was smooth. In December, 1930, she delivered prematurely a baby girl that survived.

This case illustrates a series of serious diagnostic mistakes. It was evident that the cyst, present before pregnancy, had rotated so as to lie in front of the pregnant uterus which caused me to believe at the time of my original examination that she was mistaken about the date of her last period. At the time of the original symptoms from torsion we gave too much importance to the pus cells in the urine. The urologist was positive that she had a pyelitis even though the temperature was only slightly elevated. Obviously, it would have been much better had I made a mistaken diagnosis of appendicitis. Later I should have thought of a cyst as an explanation for the apparent size of the uterus when we found a fetus of 4½ months rather than six months as expected. I consider this the most serious clinical diagnostic mistake in my entire medical practice.

However, my mistakes in this case have helped me diagnose cysts lying in front of the uterus in a number of other patients. Had we used a flat plate as an additional aid it is probable that we would have recognized the true condition prior to the vaginal hysterotomy. One should secure a flat plate whenever there may be doubt about the duration of pregnancy in cases of the type just described.

CASE 5.—Mrs. R. consulted me when she was three months pregnant. On pelvic examination it was found that the pregnant uterus was elevated by a cystic mass which seemed to be about the size of a grapefruit. It was her first pregnancy and the mass was freely movable. This ovarian cyst was removed through a Pfannenstiel incision. She continued to term and delivered normally.

CASE 6.—Mrs. M., aged 23 years, consulted me on May 1, 1944, stating that her last period began on February 28. The uterus was the size of a two months' pregnancy and in a retroverted position. Efforts to elevate it caused discomfort. On July 12, 1944, she developed severe abdominal discomfort and was sent to the hospital for observation. Her temperature was 99° F., pulse 94, and the white blood count 13,500. Her early symptoms suggested appendicitis, but after a few hours the pain localized on the left side and diagnosis of cyst with torsion was made. I had no previous suspicion that she had a cyst since it had not been palpated during my attempts to lift the uterus into a good position. On July 13, 1944, the abdomen was explored and a dark-colored cyst of the left ovary removed. Torsion had shut off the blood supply to the ovary with resulting hemorrhage into the cyst. This patient made a smooth surgical recovery, but aborted within thirty-six hours.

CASE 7.—Mrs. B. G., second pregnancy, consulted me on July 7, 1944, stating that her last period began June 5, and that she was now a few days overdue on her period. On examination the uterus was a little larger and softer than normal, but nothing abnormal was palpated in the pelvis. On Jan. 31, 1945, she reported abdominal pain located on the left side. She was ordered to the hospital for observation and a diagnosis of probable torsion of a cyst made. At operation I found torsion of the left tube which had a hydatid cyst the size of a hen's egg near the fimbriated end. The tube with cyst was removed. The following day she went into labor and delivered a premature infant that survived.

It will be noted that in three of the four cases of cyst reported, I failed to recognize the presence of the cyst during my original examination. From this experience I suspect that many cysts would be overlooked even if all women did have pelvic examinations prior to pregnancy. Nevertheless, cysts, in contrast to uterine fibroids, so frequently cause more or less serious complications during pregnancy or the puerperium that it is safer to remove them prior to the onset of pregnancy when possible. There may be a difference of opinion about removal during pregnancy in the absence of symptoms. However, it can be done safely through a Pfannenstiel incision during the fourth or fifth month. Torsion of a cyst during pregnancy or the puerperium is an indication for prompt surgery. Torsion during pregnancy may cause labor to start within a day or two with loss of the fetus if it occurs prior to viability.

Discussion

DR. LOUIS E. PHANEUF, Boston, Mass.—I am in entire agreement with Dr. Davis that most pregnancies in fibroid uteri reach the stage of viability of the fetus and that delivery takes place through the normal passages. The main indications for operative interference during pregnancy, as pointed out, are a pedunculated myoma with torsion of the pedicle and necrobiosis of the tumor. The common indication for operative interference at or near term is a fibroid blocking the birth canal.

Operating for degeneration of fibromyomas during the puerperium, while not rare, is not common. I personally do not perform multiple myomectomy at the time of cesarean section, because I believe it increases the danger of sepsis and adds to the problem of

hemorrhage. In my opinion, the intervention performed in two stages, first cesarean section, and, three to six months later, attention to the myomas, by whatever procedure is considered most suitable for the condition present, is the safer procedure.

Dr. Davis presents four cases of ovarian cysts complicating pregnancy, emphasizes the more serious problems involved with this condition, and the ever-present danger of torsion of the pedicle. As an aid in the diagnosis of ovarian cysts complicating pregnancy, a flat film of the abdomen is advised in all cases in which this complication of pregnancy is suspected.

I agree that ovarian cysts recognized during pregnancy may be safely and preferably removed during the fourth or fifth month. This obviates the possibility of torsion of the pedicle and also the possibility of a cyst blocking the birth canal.

Dr. Davis prefers the Pfannenstiel incision when operating for a myoma or for an ovarian cyst during pregnancy because "it leaves a strong abdominal wall." I prefer the median longitudinal incision which can be readily extended upward if necessary. Occasionally the size of the tumor may be underestimated, and, if it is larger than was expected, delivery through a Pfannenstiel incision may become a difficult problem and thus be responsible for the unnecessary handling of the pregnant uterus.

When care is exercised in examining a pregnant patient, pelvic tumors are not likely to be overlooked, and their timely treatment may prevent serious sequelae.

DR. R. A. CACCIARELLI, Newark, N. J.—Dr. Davis has called attention to the fact that pelvic tumors may sometimes lead to dystocia. With proper individualization of each case, there is little to fear from coexistent fibroids. During pregnancy, the obstetrician should not interfere, but he should be prepared for action when this becomes necessary. The incidence of fibroids has been estimated by Albrect and others at 1 per cent. Since many escape statistics because of small size, this figure may seem too low.

In 6,000 cases personally observed, 67 cases of fibroids complicating pregnancy were found (1.1 per cent). Of these, 57 were in primiparas and 10 were in multiparas.

Delivery by normal mechanisms of labor or assisted by low or midforceps occurred in 39, or 58 per cent. In three cases, myomectomy was done during pregnancy for necrobiosis of fibroids. Cesarean section plus myomectomy at the time of section was performed eleven times.

Many feel that myomectomy at the time of cesarean section is generally contraindicated. With this one may disagree. Many of us have successfully removed fibroids (for necrosis and pain) during pregnancy, and many fibroids have been successfully extirpated at the time of cesarean section. Cesarean hysterectomy was done in eleven cases. In three cases, cesarean section alone was done followed by myomectomy several months later. There were four abnormal fetuses delivered in the group. In two cases, puerperal necrosis of fibroids followed. In neither case was hysterectomy necessary. In one case, a full-term tubal pregnancy was also present. In another, a huge ovarian dermoid coexisted with several huge intramural fibroids.

In three cases, the fibroids were situated in the cervix or lower uterine segment. These, though less frequently seen, challenge the ingenuity and skill of the obstetrician. While it is well known that tumors of the lower uterine segment may be pulled out of the pelvis into the abdomen, by upward traction of the fundus, when this does not happen, obstruction is the result. In only one of these cases, where the fibroid was situated within the body of the cervix, was it deemed advisable to do a cesarean and total hysterectomy.

As a rule, where the fibroid is impacted in the pelvis, say in the broad ligament, and much difficulty would be encountered in its removal, it is wiser to defer surgery until some later date. Surprisingly, none of these three patients had any symptoms. The maternal mortality in this series was zero. My experience, therefore, has led me to conclude that it is not always possible to follow the same line of conduct in all cases.

Ovarian tumors on the other hand, though less frequent as a cause of dystocia, lend themselves readily to surgical removal after the third month. Twelve cases of dystocia due to ovarian tumors were seen in these 6,000 cases (1:500). Six of these were dermoid

cysts, one a fibromyxoma; one a huge chocolate cyst; one a pseudomucinous cyst; another a case of huge bilateral multiple luteomas; one case of bilateral fibroadenomas and another large simple serous cyst. Six were removed at the time of the cesarean section and five were removed between the third and fifth months. One was removed ten days post partum because of torsion.

DR. J. BAY JACOBS, Washington, D. C.—I am in accord with the previous speakers and would approach the problem in a conservative manner.

In the absence of acute signs or symptoms let the pregnancy progress and do nothing about the tumor. If the woman had a tumor, even though it looked as though it might obstruct the birth canal, it is worth waiting to see whether the presenting part would disengage the tumor. This occurs quite frequently, and the patient can be delivered through the birth canal. I can recall two cases of this type, where it appeared that the head would not engage but with effective uterine contractions the cyst was displaced and the head engaged and normal delivery occurred.

If severe complications relative to the tumor should arise at any time during pregnancy, abdominal operation is indicated. However, in the absence of severe acute symptoms, with an ample pelvis and a normal presentation, I would allow the pregnancy to continue to term feeling that labor might cause the head to displace the tumor, thus permitting delivery through the birth canal. If conservative management failed, section should be performed and the cyst removed.

DR. RUSSELL J. MOE, Duluth, Minn.—It is not always easy to make an accurate differential diagnosis of an obstructive tumor late in pregnancy or early in labor. Particularly is this true if an obstructing lesion is high in the pelvis. Lovelady and Dockerty have recently discussed a type of obstructing tumor in the posterior pelvis—a presacral neurofibroma.

I desire to report a recent case of obstruction in late pregnancy, in a 23-year-old primigravida, who had an uneventful prenatal course. During the last trimester the head did not descend into the pelvis. A lateral x-ray plate showed a mass between the promontory of the sacrum and the head. Two days before the expected date of confinement, medical induction was attempted and failed. Two days following this she had a slight amount of bleeding. On examination later it was found the head was still floating. X-ray taken at this time showed that there was still an obstructive lesion high up in the pelvis. She was four days past her date of expected confinement and it was decided to perform cesarean section. We found a large central placenta previa anterior to the promontory of the sacrum. This placenta was very large, weighing about 850 grams, and had produced the obstruction.

DR. JOHN PARKS, Washington, D. C.—One clinical point in the removal of these tumors seems to justify emphasis. If there is any remarkable torsion of the pedicle, thrombosis of the ovarian vein will occur distal to the area of obstruction. To prevent a fatal pulmonary embolus, a clamp or ligature should be placed proximal to the area of thrombosis of the ovarian vein before the pedicle is untwisted.

DR. FREDERICK H. FALLS, Chicago, Ill.—I should like to call attention to the relationship between fibroids and ectopic pregnancy. These conditions are likely to coexist and when the fibroid uterus is about the size of four or five months' pregnancy it may be very difficult to feel the tubal ectopic on bimanual examination or to determine whether or not the pregnancy is within the uterus. When sudden rupture occurs, very often the diagnosis is missed because it is impossible to feel the mass in the tube due to the enlargement of the uterus, and because the tube is located in the abdomen instead of the pelvis. One is likely to try to explain the symptoms on the basis of a torsion of an ovarian cyst or torsion of a subserous fibroid and as a result the ectopic pregnancy is not diagnosed. Sometimes these cases are treated expectantly and this conservatism may be dangerous. When in doubt, in any of these cases, the possibility of ectopic pregnancy

should be considered and exploratory operation undertaken immediately particularly if the suspicion is strengthened by the development of some of the signs of ruptured ectopic pregnancy.

There is another point which we have used in connection with the differential diagnosis of ovarian cyst and fibroid. We try to feel the uterine artery vaginally. If a hypertrophied uterine artery can be felt, and in a very large percentage of cases it can be, the tumor is probably uterine; if the hypertrophied vessel cannot be felt, it is probably an ovarian tumor. We feel that in the case described by Dr. Davis, it would be of some value to reduce the irritability of the uterus by the use of corpus luteum injections given before and after operation.

DR. CHARLES O. McCORMICK, Indianapolis, Ind.—Not infrequently we see cases of fibroid tumors of the uterus complicating pregnancy in which early hysterectomy has been advised, or delivery by section predetermined.

I think we do not sufficiently emphasize in our teaching that fibroids of the uterus do not contraindicate pregnancy, and in most instances do not warrant cesarean section.

Because fibroids often render patients relatively infertile, the salvaging of a baby in these cases is exceedingly important, and early hysterectomy rarely can be condoned.

DR. DAVIS (Closing).—It is perfectly obvious that in dealing with the tumors complicating pregnancy, one must individualize and use his best judgment. The matter of removing fibroids at the time of a cesarean section, I think, must be decided in each case. I have done it in a number of instances and do not regret removing the tumors. It is not possible always to remove all of them. I believe that we should be extremely conservative in the younger group of women in dealing with fibroids.

SALVAGE POSSIBILITIES IN THREATENED ABORTION*

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(From the Department of Obstetrics and Gynecology, Emory University School of Medicine)

FROM a perusal of the advertisements and much of the medical literature, extolling the efficacy of progestin, estrogen, and vitamins C, E, and K, in preserving pregnancy when abortion has previously occurred or is threatened, one is led to believe that such prophylactic treatment is really effective. Failure to employ these products may even invite criticism on the part of some of the profession or the patients, who may feel an important part of the treatment is being neglected.

We have gained the impression that the above claims are not justified. This belief has come about through a rigid routine of omitting all medication save simple sedatives, and noting the fact that, in a great majority of the cases, pregnancy has continued to term. Among those who aborted, adequate explanation was obtained on careful examination of the products, or in the development of complications later in the period of seven months, which, by definition, covers the period of abortion. There seemed to be only a relatively small number of cases which, theoretically, could have been benefited by the medication usually advocated.

Material

This investigation was, therefore, undertaken. Analysis was made of 1,570 consecutive cases of threatened abortion taken from the records of our private patients, in which bleeding, alone or in association with lower abdominal pain, occurred during the abortion period. All cases in which the source of the bleeding was obviously outside the uterine cavity, also bleeding known to be criminally induced, and that appearing in very scant amount at the time of the first missed menstrual period—the so-called "placental sign," were excluded.

In general, it appears that if the conception is embryologically defective or blighted, nature accomplishes its expulsion by the end of the third month. On the other hand, if the fetus is alive and developing, other factors are responsible and the symptoms of abortion develop later in the course of pregnancy.

Hence, in reporting the results of this study, it was found practical to divide the cases into two main groups: (1) those threatening to abort in the first three months, and (2) those developing symptoms from the fourth to the seventh month, inclusive.

Although the literature on the subject of threatened abortion is voluminous, a majority of the papers are devoted to the results of analyses from a pathological and therapeutic viewpoint. Very few authors have approached the subject from the angle of clinical behavior and salvage possibility. In this study, it is desired to stress the clinical behavior and salvage possibility in order to point out the futility of specific therapy aimed at the prevention of abortion. Further-

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more, it is believed that certain generalizations pertaining to the subjects of both "habitual" and threatened abortion can be made from the results of this study.

Frequency

It has been estimated that between 10 and 20 per cent of all pregnancies in women end in spontaneous abortion. Williams[1] placed the incidence at 20 per cent; both Malins,[2] and Taussig[3] at 10 per cent, and Malpas,[4] who studied 6,000 pregnancies, placed the figure at 18 per cent. Meyer[5] states that 22 per cent of fertilized ova abort.

Etiology

Valuable information regarding the etiology of abortion has been obtained by pathologic studies of the products of abortions. Streeter[6] emphasized the fact that death of the embryo usually occurs approximately six weeks before eventual expulsion by the uterus. Others have confirmed this statement. Hertig[7] found that 90 per cent of all spontaneously aborted products revealed pathologic conditions absolutely or relatively incompatible with further development of the pregnancy. In the absolutely incompatible group, consisting of blighted or pathologic ova, early death of the embryo occurs. In the relatively incompatible group, made up of monsters, hydrocephalics, etc., in spite of defects, the embryo continues to grow for a period before abortion is accomplished.

Hertig[7] found that 46 per cent of his series of abortions were due to blighted ova. Mall and Meyer[8] placed the figure at 48 per cent. Irving[9] reported that 70 per cent of abortuses were due to developmental defects, 52 per cent being due to defects of the ovum and 18 per cent to defects of all aborted products which fell in the relatively incompatible group.

The causative factors in abortion may be recurrent, or accidental. Irving[9] placed the incidence of the recurrent factor at 8.5 per cent. Malpas[4] estimated that the recurrent maternal factor was present in 1 per cent of all pregnant women. In an analysis of 6,000 cases of pregnancy, Malpas[4] showed that accidental or chance factors are not ruled out until three successive abortions or stillbirths have occurred. In other words, one cannot consider the factor recurrent and the abortion "habitual" until three consecutive interruptions have occurred. Statistically, he showed that after one abortion, 78 per cent have a normal pregnancy; after two successive abortions, 62 per cent; after three, 27 per cent, and after four only 6 per cent could be expected to carry pregnancy to term.

Effects and Results of Progestin, Estrogen, and Vitamin Therapy

The work of Frankel,[10] in 1903, who demonstrated that abortion followed removal of the corpus luteum in rabbits, gave impetus to the use of specific therapy in women presenting symptoms of threatened abortion and to the application of prophylactic therapy to those with histories of "habitual abortion." His work was confirmed and extended in studies which led to the isolation of corpus luteum hormone, progesterone. Weichert,[11] Corner and Allen,[12] and others demonstrated that progesterone, subsequent to the action of estrogen, prepares the endometrium for the reception and nourishment of the fertilized ovum. Corner and Allen[12] further showed that progestin is necessary for the conservation of early pregnancy. Reynolds and Allen[13] revealed that progestin inhibited contraction of the uterus of the rabbit in pregnancy. Hisaw[14] demonstrated in laboratory animals that the effect of posterior pituitary extract was destroyed by progestin. Falls[15] reported that progestin inhibited uterine contractions in a woman seven days post partum.

Based on the before-mentioned effects of progestin, numerous reports are found in recent literature claiming approximately 80 per cent success following

administration of progesterone in cases of both threatened and habitual abortion. Falls[15] reported successful pregnancies in 34 of 41 cases of threatened and habitual abortion treated with progestin. Eden,[16] using progesterone, claimed success in 6 of 8 cases of habitual abortion; Kane[17] treated 40 cases of threatened and habitual abortion with a combination of progesterone and thyroid extract and reported success in 36 cases. Mason[18] reported success in 30 of 34 cases of threatened abortion treated with progesterone, and claimed that 15 of 17 habitual abortion patients (one to three abortions) treated with progesterone carried pregnancy to term. Collins and associates[19] claimed success in 13 of 16 cases of threatened abortion treated with progesterone. Krohn and Harris[20] reported success in 32 of 39 cases of threatened abortion treated with progesterone. Rutherford[21] administered progestin preconceptionally to 63 women with histories of three or more consecutive abortions and reported successful pregnancies in 35 cases.

Recently the estrogens have been advocated in the treatment of both threatened and habitual abortion. Meaker[22] states, "While the direct action of estrogen on the myometrium is antagonistic to that of progesterone, there is a synergism of the two hormones in the sense that estrogen serves to support the corpus luteum and to favor the utilization, if not actually the production of progesterone." Heckel and Allen[23] were able to maintain the corpus luteum of pregnancy and inhibit abortion in rabbits by administering estrogen. Karnaky[24] reports good results in cases of threatened and habitual abortion by treatment with large doses of diethylstilbestrol. Meaker[22] suggests that these reports may indicate that "estrogen possibly can act indirectly, through an increased production of progesterone, to depress myometrial activity."

Vitamins E, C, and K have also been administered to women presenting symptoms of threatened abortion and to those classified as "habitual aborters" with claims of success equal to that following the administration of progesterone and the estrogens.

Javert and Stander[25] found that of 79 women with symptoms of threatened abortion or histories of habitual abortion, 69 per cent revealed a deficiency of vitamin C and in 72 per cent there was a deficiency of vitamin K in the blood. They claimed success in 24 of 25 women found deficient in vitamins C and K by administering these vitamins along with minerals. Others, including Vaux[26] and Hunt,[27] advocate combination of estrogen and progesterone, alone or in combination with other therapy, in the treatment of abortion.

The 80 per cent, or thereabouts, presumptive success claimed by the advocates of progesterone, estrogen, and vitamin therapy is not phenomenal when one recalls that Malpas,[4] Meyer,[5] Williams[1] and others report a spontaneous abortion rate of approximately 20 per cent. Malpas[4] has shown that following one abortion, 78 per cent of women will not repeat the loss.

Furthermore, if abortion should be delayed due to the inhibiting effect of progesterone on the uterine musculature, there is a potential danger to the woman, inasmuch as Hertig[7] has found that 66.9 per cent of abnormal and 11.6 per cent of normal ova, when aborted, showed hydatid changes. He stated that moles were found in 10 per cent of those showing hydatid change and malignancy was demonstrated in 20 per cent of moles. Also, Storch[28] found that, in early death of the embryo, atypical growths of the chorion may continue as a cystic degeneration in 75 per cent. He reports the incidence of mole to be 2.7 per cent.

At the present time, therefore, the usual treatment of threatened abortion is a combination of bed rest, sedation, endocrine and vitamin therapy. The procedure is expensive, incapacitating to the woman, and the results, as a rule, reveal the futility of such a plan of management. In most cases, the process, at the time symptoms appear, is in fact already in an incomplete rather than a threatened

phase of abortion. If the diagnosis of life or death of the embryo could be established, treatment could then be administered in an intelligent manner.

Diagnosis of Viability of the Embryo

Although several methods for the detection of a viable embryo have been described, an entirely satisfactory procedure for detecting life or death of the embryo in cases of threatened abortion is not known.

Fletcher,[29] studying vaginal smears, felt that the presence of basal-layer cells with their characteristic appearance and staining qualities were indicative of exfoliation of mucosa associated with death of the ovum. Frank and co-workers,[30] whose work was confirmed by Polonsky,[31] were the first to show that intrauterine death of the ovum is accompanied by a fall in the amount of "free" estrogen in the blood stream. Guterman[32] advocated a test for progesterone activity by estimating the level of pregnandiol excretion, which level is held to provide a reliable index to progesterone metabolism. Rutherford,[33] from a study of endometrial biopsies obtained from the lower uterine wall, was able correctly to determine life or death of the ovum in 90 per cent of cases of threatened abortion. Biological tests have proved unreliable, inasmuch as the result depends not upon life of the embryo but upon the viability of the chorionic villi. Single bimanual examinations early in pregnancy are notoriously unreliable. These methods of detecting viability of the embryo are time consuming, expensive, require special assistance, and the results are limited in accuracy.

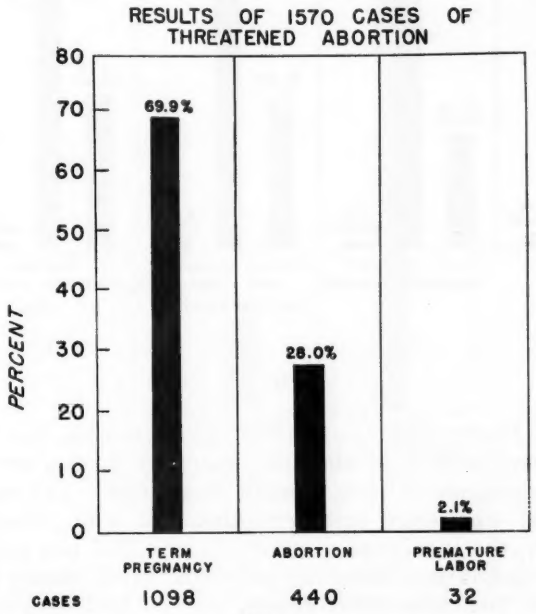

Fig. 1.

In our experience, a fairly high percentage of accuracy in determining the prognosis in such cases is possible by a careful consideration of the knowledge gained from an evaluation of symptoms and the height of the fundus over a period of time. The variable subjective symptoms of pregnancy may, or may not, be of prognostic value.

Results of Study

The results of 1,570 cases of threatened abortion are recorded in Fig. 1. Without hormones and special vitamins, other than the usual multivitamins

routinely administered during the antepartum care, 1,098, or 69.9 per cent, of the women continued to term; 440, or 28.0 per cent, aborted, and 32, or 2.1 per cent, delivered prematurely, either spontaneously or following induction of labor because of pathologic conditions threatening the safety of the mother.

Term Pregnancies.—Time and space do not permit detailed reports concerning the 1,098 women whose pregnancies were carried to term. Briefly, the incidence of fetal deformities and abnormalities of the placenta, with the exception of the circumvallate type which was encountered in 143, or 9.1 per cent, was not found increased beyond the normal expectancy. We are not able to report the incidence of circumvallate placenta among abortions but Hertig[7] mentions the condition as an etiological factor in 10 per cent of spontaneous abortions. This is in accord with our belief that the circumvallate condition is laid down early in the formation of the placenta.

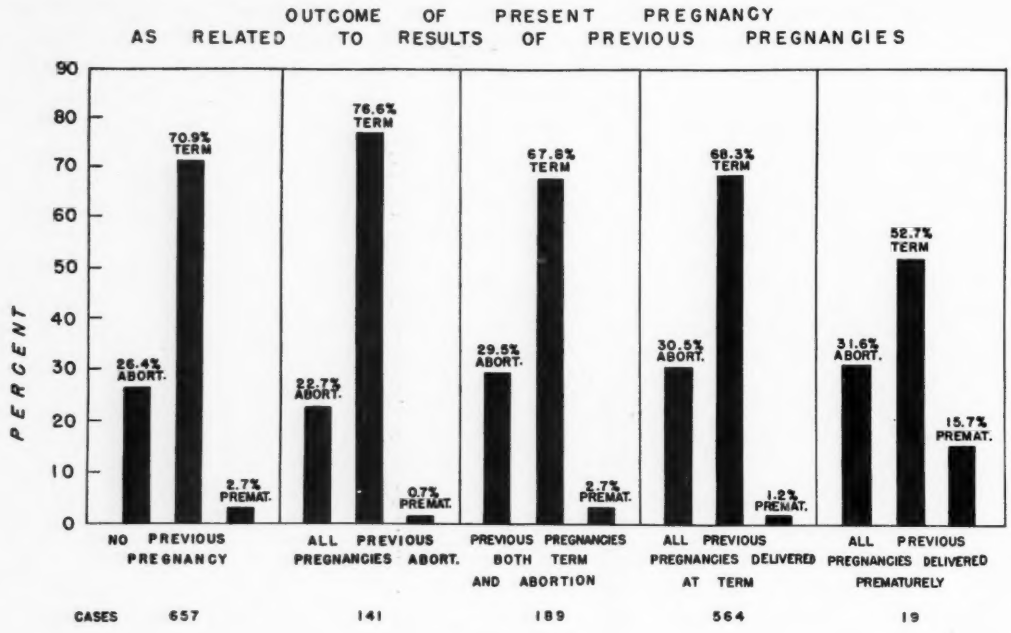

Fig. 2.

Past Obstetric Performance.—In order to determine the incidence in which chance and recurrent factors of abortion operated in this series, a study of the past obstetric performance of each woman was made. The results are shown in Fig. 2. Of the 657 who were primigravidas, but who presented symptoms of threatened abortion, the incidence of abortion was 26.4 per cent, term pregnancy 70.9 per cent, and premature labor 2.7 per cent. In a group of 141 women who had had one to four previous pregnancies, all of which had terminated in abortion, the incidence of repeat abortion was 22.7 per cent, term pregnancy 76.6 per cent, and premature labor 0.7 per cent. Had these women been treated because of having had one or more previous abortions, the lowered per cent of abortions (from 26.4 to 22.7) would have been attributed to treatment. The results of study of three other groups are shown in Fig. 1. Comparing the group of 189 women whose past obstetric performance indicated a mixture of abortions and term pregnancies with that of 564 whose past obstetric performance was perfect (one to eight term pregnancies), the difference in results was approximately 1 per cent, except for a slightly higher incidence of premature labors in the former group. In the small group of 19 women whose history

indicated that all past pregnancies terminated prematurely, 8 because of induced labor, the maximum incidence of abortion, 31.6 per cent, and premature labor, 15.7 per cent, occurred. In this group, only 52.7 per cent carried pregnancies to term. In all probability, the poor results in the latter group could be attributed to the presence of maternal pathologic conditions, such as chronic vascular disease, toxemia, etc., common to all of the pregnancies. It is significant to note that, when the past obstetric performance of a group of 141 women having had one to four abortions is compared with another group of 564 women, in all of whom the pregnancy record was perfect, the anticipated aborters had 7.8 per cent fewer abortions and 8.3 per cent more term pregnancies. This would likewise have made an impressive but misleading showing had treatment been used in the unfavorable group.

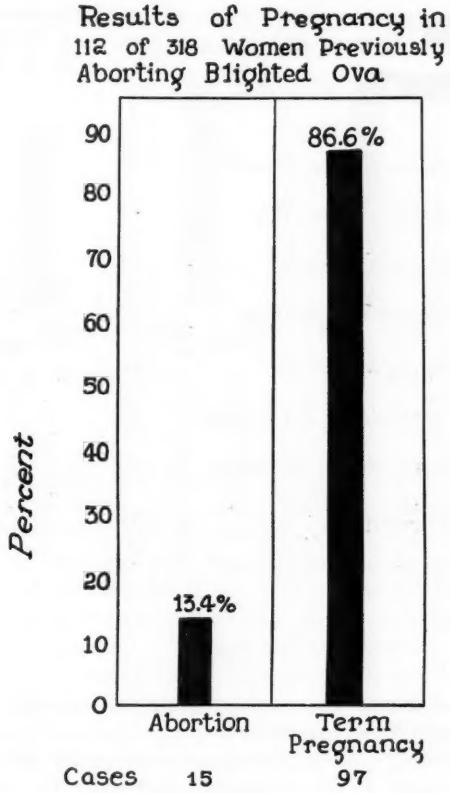

Fig. 3.

Abortions.—A total of 440, or 28.0 per cent, of the threatened abortions terminated in abortion of the product. These are subdivided according to pathologic findings as follows:

1. *Abortions due to blighted ova:* Included in this group are those cases in which the product of abortion failed to show an embryo, or contained a small amorphous mass, or those in which the embryo, stunted in development, was recognized as such but the head and limbs were hypoplastic. In this group, we have departed from the classic types defined by Mall[34] by excluding the grossly normal but macerated fetuses, often smaller than the menstrual age, without evident cause for the abortion. In Mall's[34] classification, the latter would fall into group seven of pathologic ova. We have included such products under abortions of unknown etiology.

There were 318 women, or 72.2 per cent of the total number aborting, whose products were classified as due to blighted ova as illustrated in Fig. 11.

Of 12 women presenting symptoms of threatened abortion, whose past obstetric performance ended with abortions due to blighted ova, 6, or 50 per cent, successfully carried the pregnancy to term, while the remainder again aborted blighted ova. Three of the latter subsequently carried pregnancies to term.

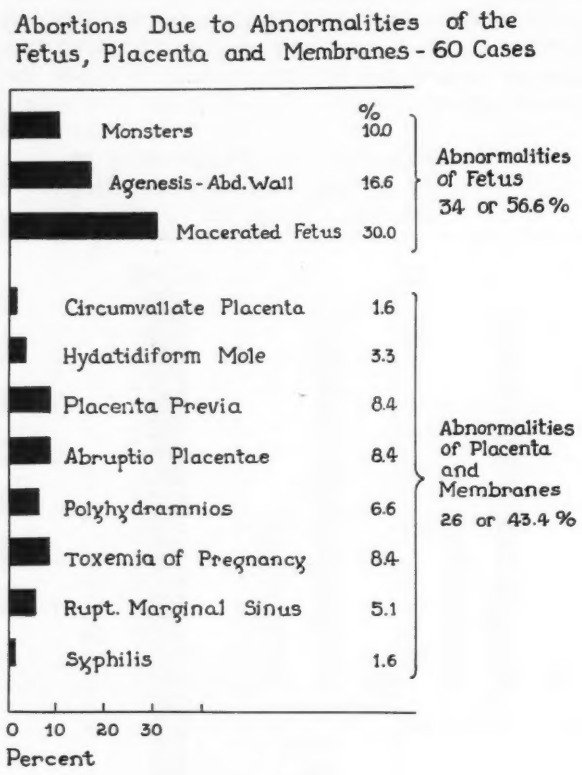
Abortions Due to Abnormalities of the Fetus, Placenta and Membranes - 60 Cases
%
Monsters 10.0
Agenesis - Abd. Wall 16.6
Macerated Fetus 30.0
Abnormalities of Fetus 34 or 56.6 %
Circumvallate Placenta 1.6
Hydatidiform Mole 3.3
Placenta Previa 8.4
Abruptio Placentae 8.4
Polyhydramnios 6.6
Toxemia of Pregnancy 8.4
Rupt. Marginal Sinus 5.1
Syphilis 1.6
Abnormalities of Placenta and Membranes 26 or 43.4 %
0 10 20 30
Percent

Fig. 4.

Of the 318 women whose threatened abortion terminated with the expulsion of blighted ova, 112 returned for care during the next pregnancy. As shown in Fig. 3, 97, or 86.6 per cent, carried the next pregnancy to term—a most encouraging result, had treatment been administered and 15, or 13.4 per cent, again aborted. Only one of the latter abortions was due to a blighted ovum, and constitutes the only incidence of 3 consecutive abortions due to this cause. It is interesting to note that the fourth pregnancy of this patient, although complicated by threatened abortion at ten weeks, was carried to term.

2. *Abortions due to developmental defects of the fetus, or pathology of the placenta and membranes:* As shown in Fig. 4, there were 60 women in this group, representing 13.6 per cent of the abortions. Definite etiological factors were present in each abortion in this group. Abnormalities in development of the fetus were found in 34, or 56.6 per cent, and pathologic conditions of the placenta or membranes in 26, or 43.4 per cent. Of the abnormal fetuses, 10 per cent were monsters, 16.6 per cent showed agenesis of the abdominal wall alone or in combination with the thorax, and 30 per cent were macerated and definitely less in size than indicated by the menstrual history. In all probability the latter correctly belong in the afore-mentioned group of blighted ova, had it been pos-

sible to make a careful examination of the macerated specimens. However, due to the recognizable body form, they are included here. The causes and incidences of abortion due to pathologic conditions of the placenta or membranes are shown in Fig. 4.

3. *Abortions of unknown etiology:* As shown in Fig. 5, there were 62 cases in which a definite cause for abortion could not be ascertained. Of this number, 11.3 per cent of the small infants lived and 33.9 per cent died. Of the stillborn fetuses 29 per cent was nonmacerated, and in 25.8 per cent maceration was present.

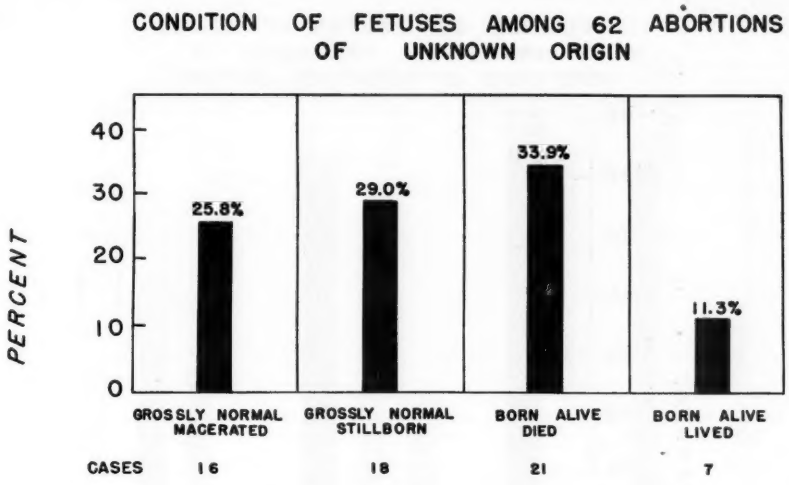

Fig. 5.

4. *Abortions due to maternal causes:* Although the cause of abortion was predominantly fetal, there were some cases which were apparently maternal in origin. Fibroid involvement of the uterus was found in 21 cases. Double uterus was found in 5 cases, in one of which the product was abnormal. Retroversion of the uterus was present in 242 cases, or 15.5 per cent. As noted in Fig. 6, the incidence of abortion was 14.9 per cent when the uterus was anteverted and 21.9 per cent when it was retroverted. This is approximately the same ratio as was found in an unpublished series of 525 consecutive cases (R. A. B.), in which the incidence of abortion was 8.7 per cent when the uterus was found anteverted in the first trimester, and 12.3 per cent when it was found retroverted. Retroversion of the uterus, therefore, is apparently a contributing factor to abortion.

Symptoms

Uterine bleeding of a brown, pink, or bright red color is the outstanding symptom of threatened abortion and was present in all cases. The types of bleeding are recorded in Fig. 7.

The type of bleeding is apparently of prognostic value. Of 452 patients in whom the initial bleeding was brown, 55 per cent aborted and, in half of these, the product was of the blighted ovum type. In only 5 cases did brown discharge appear as the initial symptom in the second trimester. In 1,001 cases in which the initial bleeding was bright red, often of considerable amount, occasionally tapering off to brown before recurring as bright red, only 10 per cent aborted, and 87 per cent continued to term.

It would seem, therefore, that brown discharge in the first trimester usually signifies an inevitable abortion of a nonviable product undergoing a gradual loosening at the placental bed, whereas sudden bright red discharge signifies

slight separation at some point on the placental margin, and is more often compatible with continuation of the pregnancy. In this case one may predict the finding of gray puttylike fibrin adherent to the membranes near a point on the margin of the placenta at term. We, therefore, may have more assurance that pregnancy will continue if the initial bleeding is bright red than if it is brown.

Occasionally the initial bleeding is a mixture of brown and bright blood. In a group of 117 cases, showing this type of bleeding in the first trimester, 66 per cent ended in abortion and half of these were of the blighted ovum type. Three per cent delivered prematurely and only 31 per cent continued to term.

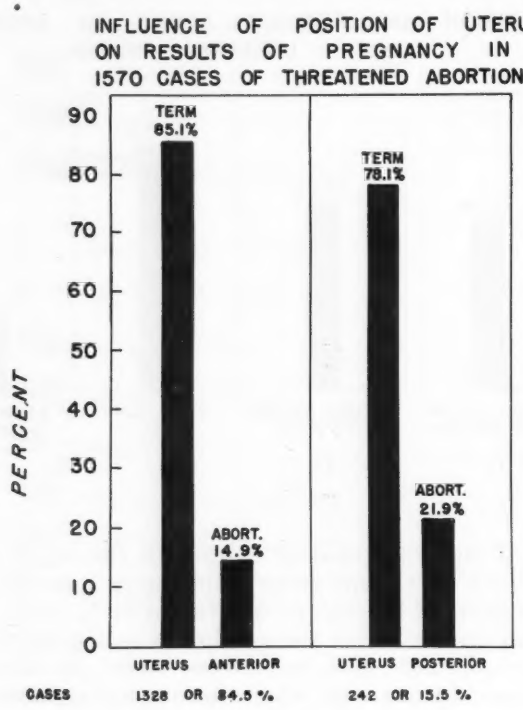

Fig. 6.

Some significance may be attached to the manner in which the bleeding manifests itself. Among patients aborting blighted ova, 95.9 per cent experienced only one episode of bleeding of gradually increasing amount and color. Among patients aborting developing fetuses, 48.3 per cent experienced multiple episodes of bleeding before completing the process.

In general, bleeding is the initial symptom of early abortion and pain the initial symptom of late abortion. In this series, as shown in Fig. 8, pain preceded bleeding in 8 per cent, accompanied it at the onset in 9 per cent, and followed it in 75 per cent. In 337 patients in whom pain was associated with continued or closely spaced episodes of bleeding, 100 per cent aborted.

Bleeding begins at an earlier stage if the ovum is blighted. The average time of appearance of bleeding due to blighted ova was approximately eight weeks. When the fetus was recognizable, the average time was sixteen and one-half weeks. The average time between the appearance of bleeding and eventual abortion of a blighted ovum was thirteen days, but in case of a recognizable fetus it was fifty-four days.

As seen in Fig. 9, an analysis of 1,570 patients with untreated threatened abortion showed 1,098, or 69.9 per cent, continued to term; 318, or 20.3 per cent,

aborted blighted ova; 60, or 3.8 per cent, aborted products showing gross anomalies of the fetus or pathologic conditions of the placenta or membranes incompatible with viability of the fetus, and 32, or 2.1 per cent, aborted spontaneously or artificially because of toxemia, abruptio placentae, placenta previa, or ruptured marginal sinus threatening the safety of the mother.

There were 62 cases, or 3.9 per cent, in which the cause of the abortion could not be determined. Of these fetuses, 7 survived and 21 died. Thirty-four were grossly normal, including the 16 which were macerated.

Therefore, only 3.9 per cent of 1,570 threatened abortions could theoretically have been benefited by specific hormone or vitamin therapy, and possibly salvaged.

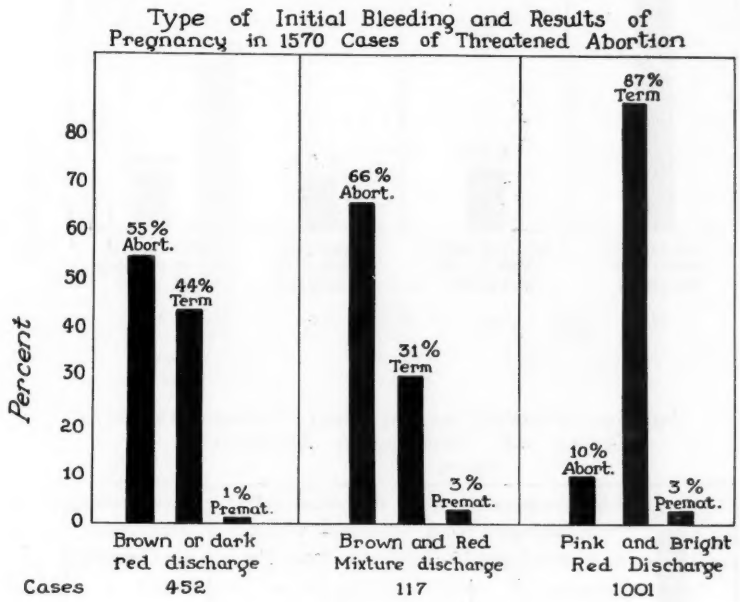

Fig. 7.

Management

When abortion is threatened, especially in the first trimester, both the physician and the patient are vitally interested in determining whether the pregnancy will carry on or will be aborted. In a majority of cases, a determination of the urinary pregnandiol level will supply the answer, a low-level indicating a decrease in the normal progesterone formation and degenerative changes of the endometrium. Replacement therapy with estrogen and progesterone cannot be expected to restore diseased villi. Recall that, in the majority of instances, the threatened abortion is due to a blighted ovum which, as a rule, ceased development six weeks prior to symptoms.

The common practice is to institute hormone and vitamin therapy at once, either in faith or in conformation to accepted practice, admitting that the patient is hormone-wise and expects something to be done.

It is our belief and practice that a simple explanation of what is in the background of early abortion serves to satisfy the patient and reconcile her to a plan of therapeutic nihilism. A variable period of time will be necessary to note the trend of the signs and symptoms.

Meanwhile, reasonable activity as to meals and bathroom privileges is permitted. If the pregnancy is of less than two months, the patient may be allowed

to abort at home, but is previously supplied with a pain-relieving agent and Ergotrate, should discomfort and bleeding prove to be more than anticipated at this stage. She is advised to save the fleshy product of abortion, preserving it in half-strength rub alcohol for further examination.

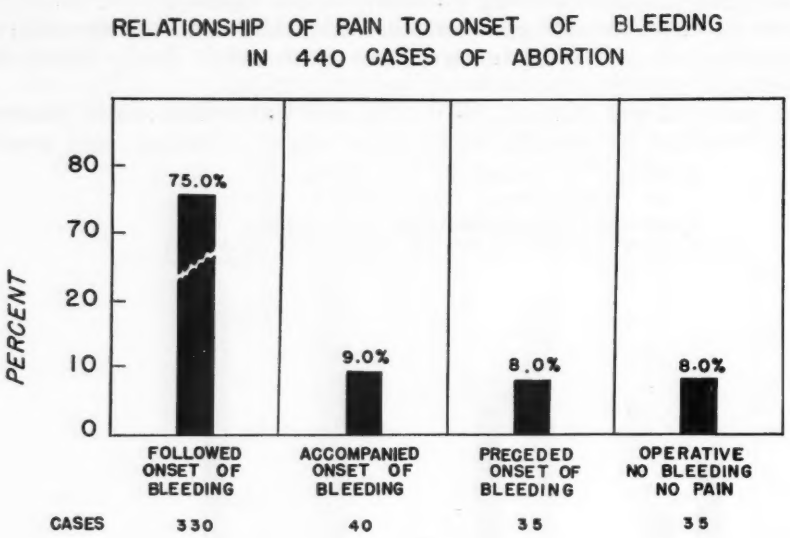

Fig. 8.

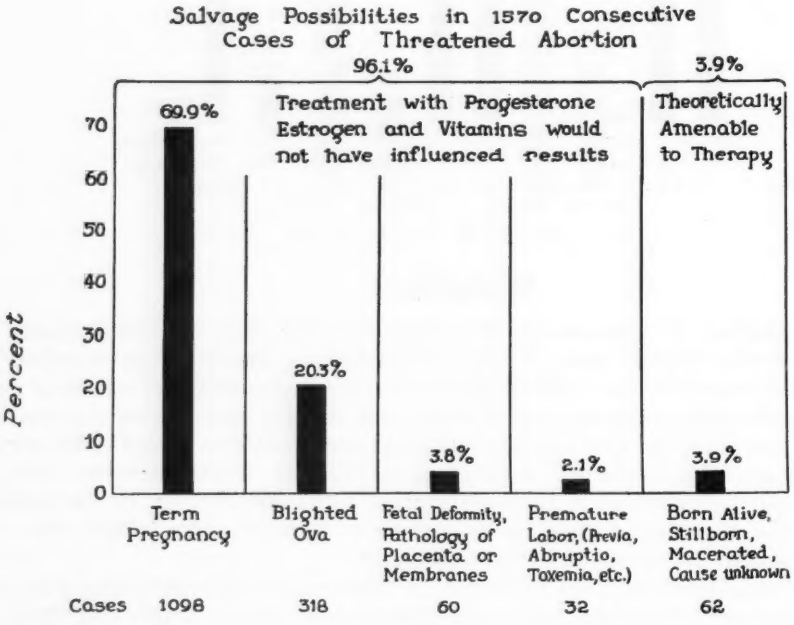

Fig. 9.

If the pregnancy is over two months' duration, she is advised to enter the hospital when the amount of bleeding requires frequent change of pads, since excess bleeding, pain, or retention of products will require hospital facilities. If rupture of the membranes, dilatation of the cervix, excessive bleeding, or a distinct deficiency in size of the uterus indicates inevitable abortion, one-half

ampule of pituitary extract is given hourly, or more frequently, for four to six doses, by which time abortion has usually occurred. Unusually free bleeding may be controlled by intravenous administration of four minims of Pitocin. The products are allowed to extrude spontaneously, as checked by rectal examinations, unless found to be hanging loosely in the cervical canal when it may be possible to lift them out. A course of Ergotrate is given during convalescence and the patient is usually discharged in two or three days.

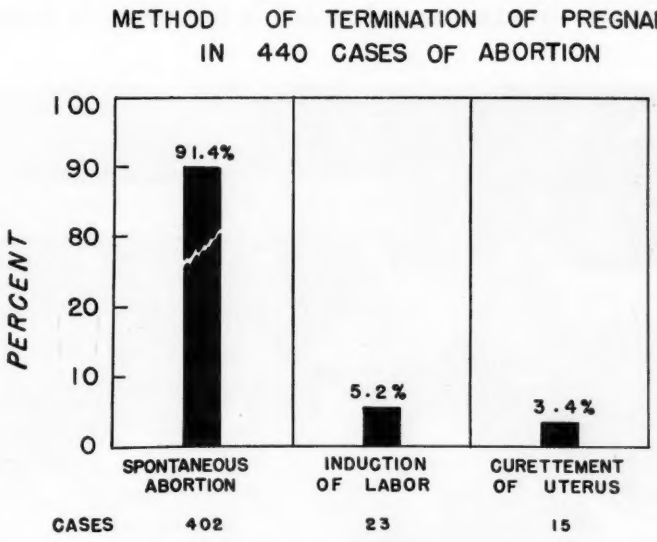

Fig. 10.

As to the manner of termination of pregnancy in 440 cases of abortion in this series, as shown in Fig. 10, 15, or 3.4 per cent, were removed by curettement, 23, or 5.2 per cent, induced, and 402, or 91.4 per cent, aborted spontaneously. Except in the early years of practice, the management has been conservative and not operative. There was no mortality and only one patient had a significant degree of fever.

When patients register for the first prenatal visit, within the first trimester, particular note is taken of the height of the fundus. Whether or not bleeding occurs before the next visit, four weeks later, the height of the fundus is again noted. A deficiency in enlargement is at once recognized as indicating probable abortion.

Bearing in mind occasional obvious factors which influence the height of the fundus at various stages of pregnancy, the application of Bartholomew's[36] "rule of fourths," Fig. 12, has proved most helpful. Deficiency in height of the fundus is readily recognized and furnishes supportive evidence of blighted ovum and inevitable abortion. However, if the uterus continues to enlarge, consistent with the "rule of fourths," even though bleeding may continue intermittently to the fourth or fifth month, pregnancy may continue to term.

Discussion

It is obvious that nothing can be done for fertilized ova in which the early stages of cell division show a disorderly arrangement incompatible with further development. This has been shown by Rock and Hertig,[35] who discovered and diagnosed such specimens collected from uteri removed for various therapeutic reasons from women with normal fertility, who, with one exception, kept a record of coital dates preceding operation. Twelve, or 47 per cent, of 26 very

early embryos were abnormal in either trophoblastic or dermal tissue or in both. The inner cell mass or embryonic disc was absent in two imbedded specimens.

Granting that the product of gestation is continuing to develop when it reaches the uterine cavity in very early embryonic life, is it not purely theoretical that the implantation bed is of greater importance than the villi upon which the embryo will soon be completely dependent? Hormone and vitamin therapy is given on the theory that the implantation bed will be structurally and physiologically in the most favorable state when the ovum imbeds. However, implantation must have already taken place before pregnancy is diagnosed and therapy begun.

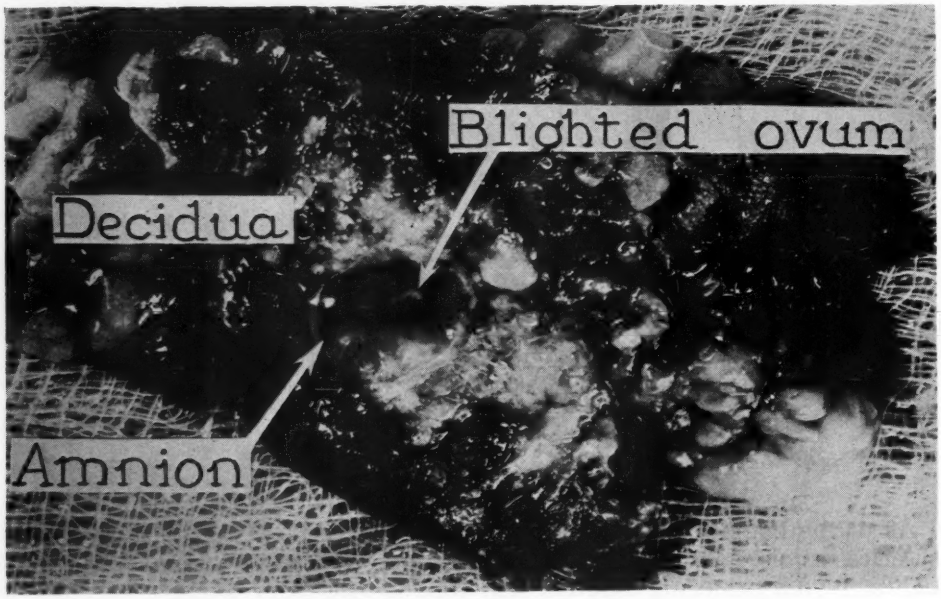

Fig. 11.

Of much greater importance is the ability of the villi to erode the decidua and create a rich maternal blood supply. If the villi are slow to vascularize or even fail in this important process, they become cystic and the embryo dies from lack of nourishment. That early cystic or hydatid change is frequently found in the early formation of the placenta, has been shown by Hertig.[7] If the villi make a more important contribution to early embryonic growth than the decidual portion of the early placenta, one cannot expect much effect from hormone and vitamin therapy.

Referring to Fig. 2, the significant fact is shown that among women showing symptoms of threatened abortion, those presenting a previous perfect obstetric history (564 cases) had a 7.8 per cent higher incidence of abortion of the present pregnancy than those in whom all previous pregnancies had ended in abortion (141 cases). This single fact seems to indicate that the emphasis placed upon the so-called "recurrent" maternal factor in abortion is unwarranted and that a factor peculiar to and inherent in each fertilized ovum is responsible for the abortion.

The increased irritability of the uterine muscle is more likely the response to an abnormal ovum or embryo than an antecedent irritability which progesterone may neutralize. Considering the fact that Hertig[7] found 66.9 per cent of abnormal and 11.6 per cent of normal ova to show evidence of hydatid change and moles were found in 10 per cent of those presenting hydatid change and,

furthermore, that 20 per cent of moles show some degree of malignant change, is it not objectionable to administer any treatment which will dull the irritability of the uterus and therefore permit prolonged retention of a product which has dangerous potentialities?

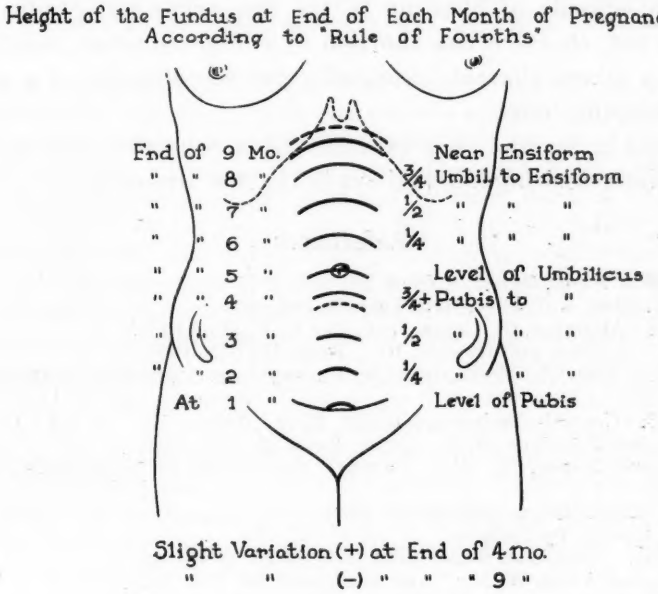
Height of the Fundus at End of Each Month of Pregnancy
According to "Rule of Fourths"
End of 9 Mo.
" " 8 "
" " 7 "
" " 6 "
" " 5 "
" " 4 "
" " 3 "
" " 2 "
At 1 "
Near Ensiform
¾ Umbil. to Ensiform
½ " " "
¼ " " "
Level of Umbilicus
¾ Pubis to "
½ " " "
¼ " " "
Level of Pubis
Slight Variation (+) at End of 4 mo.
" " (-) " " " 9 "

Fig. 12.

Summary and Conclusions

1. The general assertion and acceptance of the prophylactic value of hormone and vitamin therapy in threatened or habitual abortion are apparently unwarranted.

2. Such therapy is theoretically designed to benefit the maternal factor, by favoring a healthy implantation bed and lessening uterine irritability, but could not influence the fetal factor of abnormal ova or embryos, or changes of hydatid nature in the villi, which are already present before therapy can be administered.

3. An analysis of 1,570 untreated cases of threatened abortion showed only 62, or 3.9 per cent, which could theoretically have been prevented by hormone and vitamin therapy.

4. Abnormal or "blighted" products constituted 318, or 72.8 per cent, of the abortions; 60 cases, or 13.6 per cent, could be attributed to anomalies of the fetus, pathologic conditions of the secundines or maternal complications, and 62 cases, or 14.1 per cent, could not be attributed to any definite cause.

5. In this series, 564 patients with threatened abortion presented completely successful records of past pregnancies, but the incidence of abortion of the present pregnancy was 7.8 per cent higher than in a group of 141 patients in whom all the previous pregnancies had aborted. These results emphasize a fetal rather than a maternal cause.

6. Initial brownish discharge later becoming red portends abortion more frequently than initial red discharge later becoming brown.

7. Bleeding usually precedes pain in abortions of the first trimester; pain usually precedes bleeding in abortions of the second trimester.

8. A single episode of bleeding in the first trimester, gradually changing from brown to red, characterizes abortion of a blighted ovum: multiple episodes of bleeding of a mixed character generally precede abortion of a developing or previously developing fetus.

9. The "rule of fourths" is a valuable aid in recognizing the deficient height of the fundus characterizing blighted ova in the first trimester.

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Discussion

DR. BERNARD J. HANLEY, Los Angeles, Calif.—Admittedly there is no specific treatment for threatened abortion. Dr. Colvin's treatment consisting of bed rest and sedation is exactly what most of us would like to prescribe for our patients, but few of us have the courage to do so for fear of criticism by other physicians or by the patient and her relatives and friends. Like many other obstetricians, I have run the gamut of all types

of medication. At the present time the giving of estrogen in the form of diethylstilbestrol seems to be the most popular method of treatment. During the past two years I have run a fairly large series of these cases in which doses of 15 mg. to 100 mg. of stilbestrol daily have been given, along with an equal series in which no medication was given. Urinary pregnandiol determinations were made at various intervals throughout the pregnancy. I was not able to show that the giving of estrogen increased the amount of pregnandiol excretion, and in fact a fairly large number of cases showed a lesser output than in the control cases.

Furthermore, the proportion of these cases salvaged was not any greater than those in which no medication was given except bed rest and sedation. My results in the use of stilbestrol are at odds with those of other men using this method of treatment. Perhaps stilbestrol may have some other beneficial effects. The prophylactic giving of estrogen to a pregnant woman who may have had one, two, or three abortions may or may not be logical but certainly, if the pregnancy goes to full term, and if there were no signs or symptoms of threatened abortion, then giving this treatment credit for preserving the pregnancy is only *post hoc* reasoning. I believe many of these published good results are just that. Dr. Colvin makes this terse statement which seems to me to be the crux of the entire problem in the treatment of threatened abortion. He says, "In most cases, the process, at the time symptoms appear, is in fact already in an incomplete rather than a threatened phase of abortion. If the diagnosis of life or death of the embryo could be established, treatment could then be administered in an intelligent manner."

According to his results as shown in Fig. 9, 69.9 per cent of the patients went to full term with no medication except bed rest and sedation. Twenty-six and two-tenths per cent were accounted for by abortion (blighted ova, fetal deformities, placental deformities), premature labor, and placental accidents. That leaves only 3.9 per cent for which other forms of treatment may have been of some advantage. The saving of four more fetuses out of one hundred pregnancies is certainly commendable, and I am vitally interested in it. However, the patients should not be hoodwinked into believing that the giving of expensive injections, vitamins, or other medications will surely lead to full-term delivery of a normal infant.

DR. NICHOLSON J. EASTMAN, Baltimore, Md.—The late Dr. George L. Streeter showed on the basis of the vast number of embryos in the Carnegie collection, together with case histories, that in spontaneous abortion a surprisingly long interval intervenes between the death of the fetus and the expulsion of the dead conceptus. Indeed, he showed that this interval averages three weeks, and that it is not at all unusual for it to be extended to six weeks. This means that when a patient bleeds in early pregnancy and then aborts, the fetus is already dead in the majority of cases when the bleeding starts. In Dr. Colvin's series this group apparently made up about 69 per cent of all his patients who bled in early pregnancy. Obviously, treatment in this group of cases is futile. In 30 to 50 per cent of cases the bleeding may be due to decidual seepage, to erosion of the cervix or to a polyp, and, in the main, these causes can be looked upon as fairly benign in so far as the imminence of abortion is concerned. That leaves us with a small group of cases, 3.9 per cent in Colvin's series, in which there is evidence that therapy may do some good. These are apparently cases in which minute marginal placental separation occurs and then seals over. Some probability is lent to this view by the fact that in many cases of placenta previa there is an early history of bleeding. In other words, the therapy of threatened abortion is avowedly futile in about half the cases because the fetus is already dead. In another 30 or 40 per cent it is unnecessary because the causes of bleeding require no treatment. Hence, there remains only a small percentage of cases in which therapy may be effective.

Dr. Colvin's paper bears out these general contentions and shows the futility of treatment in many cases of threatened abortion. Nevertheless we have to face the fact that we must treat nineteen or twenty cases needlessly in order to help the occasional case in which various therapeutic measures may be effectual.

DR. OTTO H. SCHWARZ, St. Louis, Mo.—I was interested in the predictions that were made as to the vaginal discharge. If it was brown, these cases were considered unfavorable, and if the discharge was red, they were considered more favorable. Recently, I went over some cases with Everett in Baltimore, and he felt he could tell by the character of the vaginal smear whether a patient, in the case of threatened abortion, is going to abort or not. The details of what this difference is I do not know, but it is very striking. This means that if Everett's observations are accurate, those cases that are favorable would be the cases that you may help with hormone and/or vitamin therapy.

DR. WARD F. SEELEY, Detroit, Mich.—Inasmuch as the urgent need for the reduction of maternal mortality has been met fairly satisfactorily in the last decade, it is reasonable that the efforts of obstetricians should turn to the next important problem, that of fetal mortality. From the fact that approximately 20 per cent of all pregnancies terminate in fetal death, Dr. Colvin's paper on fetal salvage in threatened abortion is important.

What can be done to salvage threatened abortion? In the light of the work of Mall and others, is it advisable to institute heroic measures? Can the high unpreventable abortion rate be considered as a conservative means of limiting an ever-increasing population? Is the use of endocrine and vitamin products attended with actual success to a degree sufficient to make their employment indicated? What effect do nutritional defects in the mother have in production of malformations and deformities in the offspring?

Without going into detail, Dr. Colvin's paper shows the futility of relying on the endocrine and vitamin products for the treatment of threatened abortions in a large percentage of cases. Rest, sedation, and the correction of retrodisplacements have given him as good or better results as those obtained by the advocates of indiscriminate endocrine therapy. However, as a prophylactic measure, there seems to be at least some basis for the idea that vitamin and endocrine deficiencies should be corrected. Waltenwyl states that the normal tocopherol level in pregnant serum is 400 to 1,500 gamma per cent, and in pregnant women with abortion histories the content is five-sixths less. It would seem reasonable to enrich the diet of these women with vitamin E. In pregnant women with delayed prothrombin time and a history of abortion, the use of vitamin K has many advocates. In other words, as Dr. Colvin has shown, there is a small number of cases that may be salvaged by prophylactic use of the vitamins, endocrines, and adequate protein intake.

In order that any form of prophylactic treatment be successful it should be begun before pregnancy occurs, for as Dr. Colvin has pointed out, symptoms do not manifest themselves in many cases until *after* fetal death. To carry out this regime is at best difficult and in many cases impractical. No one has yet proved a relationship between congenital defects and maternal nutritional deficiency.

Our management is somewhat more radical than that described. In early abortion if the products of conception are not promptly expelled, we do not hesitate to curette. Prolonged bleeding is thus avoided and the period of disability definitely shortened.

Dr. Colvin's careful study confirms our impression that endocrine and vitamin therapy is useless in a high percentage of cases.

DR. COLVIN (Closing).—The data presented represent uncorrected figures. However, included in the 62 cases (Fig. 9) are 18 cases in which the fetus was macerated and considerably smaller than expected by the menstrual history, which could have been included as pathologic ova under Group 6 or 7 of Mall's classification. Had such an adjustment been made, the salvage possibilities would have been further reduced.

EARLY EXTRAUTERINE PREGNANCY*

D. Nelson Henderson, M.D., and John L. M. Bean, M.D., Toronto, Ont.

(From the Department of Gynaecology and Obstetrics, University of Toronto)

THIS paper is a review of 302 cases of early extrauterine pregnancy treated on the public gynecological wards of the Toronto General Hospital. The pregnancies were tubal in situation in all but two cases, and in these two the site of implantation was the left ovary.

Etiology and Pathology

While a great variety of causes have been suggested to explain tubal pregnancy, probably the most important single cause is previous tubal inflammatory disease. In 184 cases, tubal architecture was sufficiently undisturbed by the pregnancy and resulting hemorrhage to permit histological study of sections taken distant to the site of implantation. Twenty-seven per cent of these tubes showed evidence of chronic follicular salpingitis characterized by scarring of the wall and plicae of the tube with formation of multiple pseudo gland spaces lined by tubal epithelium. In three cases, the salpingitis was tuberculous in origin, and in one of these a second ectopic pregnancy occurred in the other tube one year later. As salpingitis is so frequently a bilateral disease, it was not surprising to find that, to our knowledge, repeated tubal pregnancy occurred in twenty-six cases, or approximately 9 per cent.

Endometrium-like metaplasia of the tubal mucosa which might increase the receptivity of the tubal mucosa to the ovum was not observed in any instance. Decidual reaction in the stroma of the tubal folds was not infrequently described in the pathological reports, but, when the sections were reviewed, the changes were those of edema and hypertrophy of the fibrous stroma rather than a true decidual transformation as is so frequently seen in the tubes and ovaries in full-term pregnancy.

Other causes for the tubal implantation, such as tubal diverticula, stretching of the tube over ovarian or intraligamentous tumors, were not observed. It would appear that factors other than tubal inflammation that lead to delay or arrest of the ovum in its passage through the tubal lumen are probably physiological disturbances not recognized by ordinary histological methods of examination.

Decidual transformation of endometrium probably occurs in all cases of tubal pregnancy in which nidation remains undisturbed. However, due to the insecurity of the pregnancy in the tube and the frequency with which endometrial desquamation and bleeding begin within a few days of the next expected menstruation, it is not surprising that decidual change in the endometrium was infrequently observed. In 43 cases in which the endometrium was available for histologic examination, a decidual reaction was observed in only seven instances. In four additional cases, however, a more or less complete decidual cast of the uterus was passed.

Intraperitoneal tubal rupture occurred almost as frequently as internal rupture or abortion. The former, however, was more frequently associated with

*Presented at the Sixtieth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 8 to 10, 1949.

sudden massive hemorrhage and shock. Of the 91 cases in which severe shock from hemorrhage occurred, tubal rupture was responsible in 62 instances, whereas, in the remaining 211 chronic cases, tubal rupture occurred only 56 times. In only one case did intraligamentous rupture take place and there were only five instances of tubal mole formation. When it is appreciated that these cases have been collected over a period of fifteen years, during which time many hundreds of laparotomies for gynecological reasons have been performed, it must be concluded that the formation of a tubal mole is a rare occurrence.

TABLE I. TERMINATION OF PREGNANCY

	ACUTE GROUP	CHRONIC GROUP
Intraperitoneal rupture	62 cases	56 cases
Internal rupture or abortion	20 cases	91 cases
Tubal mole	0 cases	5 cases
Ovarian pregnancy	1 case	1 case
Undetermined	8 cases	58 cases
Total	91 cases	211 cases

No case of simultaneous bilateral tubal pregnancy or tubal and intrauterine pregnancy occurred. There were, however, two cases of ovarian pregnancy, both involving the left ovary. In one, the tube was removed along with the ovary and was histologically normal. In the other, the tube was grossly normal and was not removed. The first specimen (Fig. 1) appeared to be that of a normal ovary containing a corpus luteum which had ruptured. On more careful examination, however, delicate chorionic villi could be observed protruding at the site of rupture. No fetus was evident, and the whole hemorrhagic follicle measured only 3 cm. in diameter. Histological examination revealed branching villi invading the ovarian stroma and adjacent lutein cells. The pregnancy in the second specimen (Fig. 2) had progressed much further, a fetus measuring 3 cm. in length was present, and the whole hemorrhagic sac measured 8 cm. in diameter. Histologically, ovarian stroma could be demonstrated partially surrounding the gestation sac, but no lutein cells were evident in any of the sections.

There was one case of tubal chorionepithelioma. The pathological specimen consisted of large and small broken fragments of blood clot forming a mass of approximately 10 cm. in diameter. The ovary was covered by blood and contained a large corpus luteum. The ampullary portion of the tube was distended by blood clot and the fimbriae could not be identified. Study of many sections revealed masses of syncytial and Langhans' cells, but no formed villi (Figs. 3 and 4). A diagnosis of chorionepithelioma was made with some reluctance, but the subsequent clinical course of the patient confirmed it. The Aschheim-Zondek test for pregnancy remained positive after operation, and the patient eventually developed a secondary tumor nodule in the vagina (Fig. 5). This was excised and treated by interstitially placed radium needles. Following this, the patient became comatose and developed thrombosis of the left external jugular vein. This was considered to be due to secondary tumor. Eventually, however, the Aschheim-Zondek test became negative and the patient recovered completely and was alive and well five years later. This case was reported in 1939.[1]

Clinical Features

For the purpose of clinical analysis and assessment of diagnostic errors, the cases have been divided into two groups. The first group comprises the patients who were in a severe degree of shock which developed either before or after admission to hospital. These were considered acute cases. The remainder

of the patients who were not in shock were classified as chronic cases. Many patients in the latter group had extensive intraperitoneal hemorrhage, but the blood loss was gradual rather than sudden, so that the blood volume was maintained and shock did not develop. A history of a delayed or missed menstruation

Fig. 1.—Primary ovarian pregnancy. The ovary contained a hemorrhagic follicle 3 cm. in diameter which on section was lined by lutein cells and filled with blood clot and multiple chorionic villi.

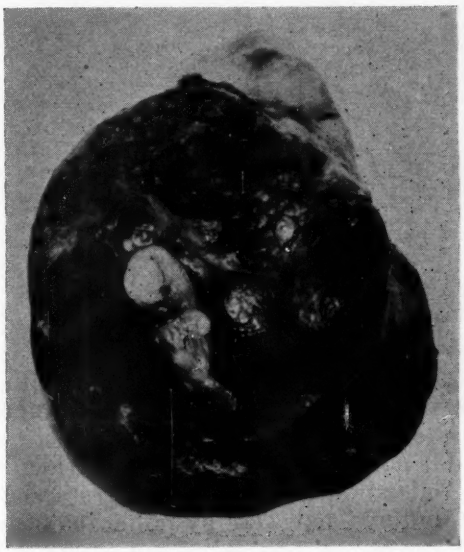

Fig. 2.—Primary ovarian pregnancy. A fetus nearly 3 cm. in length is shown. The whole hemorrhagic sac measured 8 cm. in diameter.

is usually cited as an important symptom in the diagnosis of ectopic pregnancy, yet it was present in slightly less than half of the cases in this series. Of the 259 cases in which the menstrual history was recorded, 159 patients developed vaginal bleeding before or at the expected time of menstruation.

TABLE II. ONSET OF VAGINAL BLEEDING AFTER THE LAST NORMAL MENSTRUATION

	ACUTE GROUP	CHRONIC GROUP
Under 28 days	3 cases	50 cases
28 to 34 days	26 cases	56 cases
Over 34 days	50 cases	74 cases
Total	79 cases	180 cases

In many instances the bleeding resembled the onset of a normal menstruation but continued as dark spotting rather than free bleeding. Occasionally, however, the blood loss was excessive enough to suggest the abortion of an intrauterine pregnancy. On the other hand, 26 patients, or approximately 9 per cent, showed an absence of vaginal bleeding; 12 of these patients were in the acute group and 14 in the chronic group.

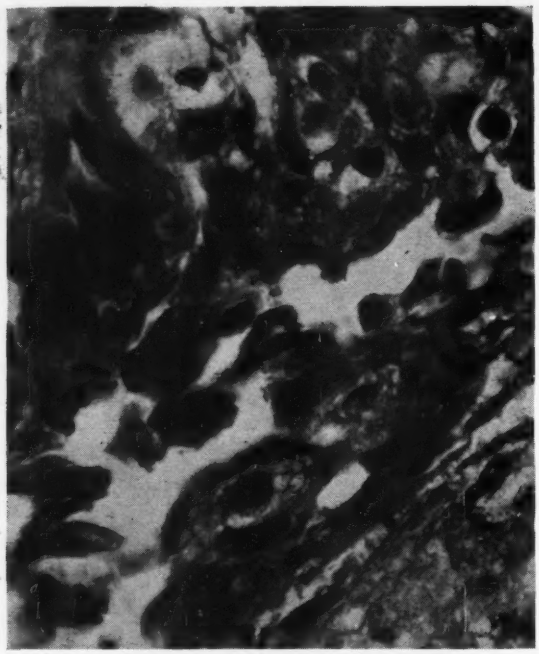

Fig. 3.—Chorionepithelioma of the tube. Photomicrograph showing both syncytial and Langhans' cells with syncytial cells predominating. (×450.)

Gastrointestinal symptoms were surprisingly common. Nausea, vomiting, or diarrhea was complained of by 86 patients, or nearly 30 per cent.

Practically all patients complained of abdominal pain, but it varied greatly in severity and location. Frequently the pain was generalized over the whole abdomen, and often associated with pain in one or other scapular region. The pain, when localized, did not always indicate upon which side the ectopic pregnancy was situated. Abdominal distention, hyperesthesia, and rebound tenderness were all frequent findings, but were by no means constant even when large amounts of blood were present in the peritoneal cavity. The wide variation in physical signs on abdominal examination, when considerable free blood was present, was puzzling. Shoulder pain was complained of by one patient in four, and syncope or collapse occurred in 60 per cent of the cases.

The most constant findings on pelvic examination were vaginal bleeding, pelvic tenderness, and an extrauterine mass. The pelvic tenderness varied greatly

in severity. In 28 per cent of the acute cases and 22 per cent of the chronic group, no extrauterine mass was palpable, and pelvic tenderness remained the only positive finding on examination.

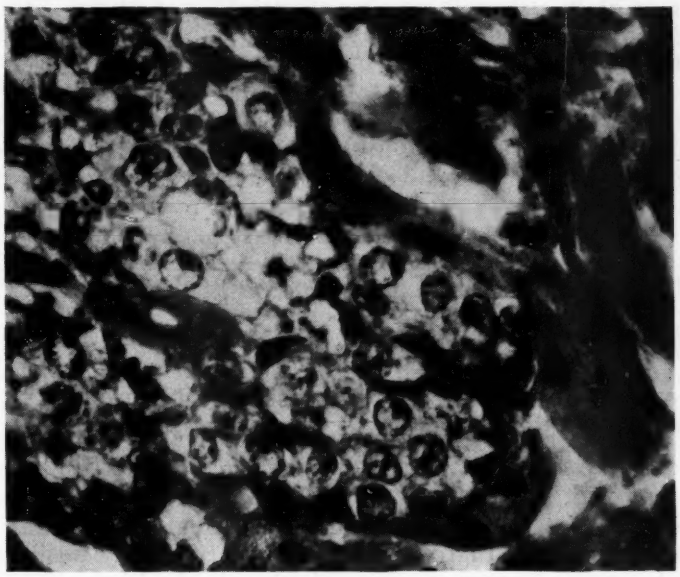

Fig. 4.—Chorionepithelioma of tube. Section from another area showing predominance of Langhans' cells. (×450.)

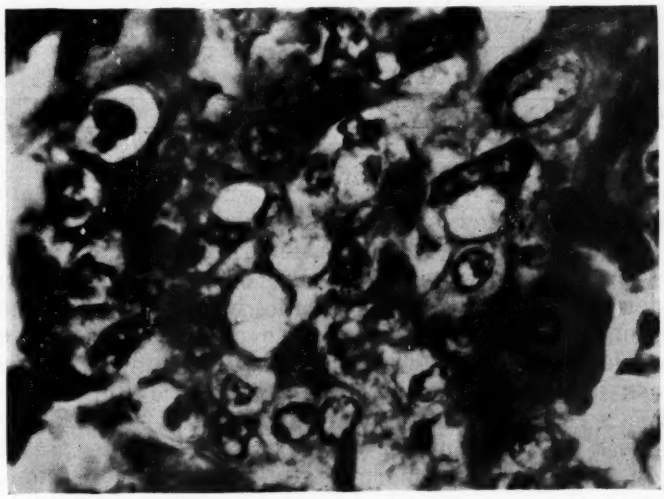

Fig. 5.—Secondary chorionepithelioma of vagina. (×450.)

Laboratory Aids in Diagnosis

Temperature, white blood count, hemoglobin estimation, and sedimentation rate are routinely recorded on all gynecological cases. The results of these are tabulated in Tables III, IV, and V.

In brief, it may be stated that in the majority of cases, temperature readings were below 100° F., white blood counts above 10,000, and sedimentation rates within normal limits. The majority of the high white counts occurred

TABLE III. TEMPERATURE

TEMPERATURE	ACUTE CASES	CHRONIC CASES
Below 98° F.	24 cases	8 cases
98 to 99.9° F.	45 cases	162 cases
100° F.	22 cases	41 cases
Total	91 cases	211 cases

in the acute group of cases. It was noted that a high white blood count and a normal sedimentation rate were highly suggestive of blood in the peritoneal cavity. Hemoglobin estimations were 70 per cent or more in over half the cases.

TABLE IV. WHITE BLOOD COUNT

WHITE BLOOD COUNT	ACUTE CASES	CHRONIC CASES
Under 9,900	9 cases	89 cases
10,000 to 14,900	24 cases	72 cases
15,000 to 19,900	24 cases	25 cases
20,000	30 cases	18 cases
Total	87 cases	204 cases

The modified Aschheim-Zondek or other urine tests for pregnancy were frequently employed, but were of only minimal help in diagnosis. Such tests did occasionally assist in differentiating inflammatory adnexal masses from those due to pregnancy. In three instances, persistently positive tests led to a diagnosis of ectopic pregnancy in patients who had been curetted with the erroneous diagnosis of incomplete abortion.

TABLE V. SEDIMENTATION RATE

SEDIMENTATION RATE	ACUTE CASES	CHRONIC CASES
Normal	34 cases	120 cases
Increased	17 cases	46 cases
Total	51 cases	166 cases

Surgical Aids in Diagnosis

Exploration of the pouch of Douglas, either by aspiration through the posterior fornix by a large-bore needle or posterior colpotomy, was employed in 126 cases. Aspiration of the cul-de-sac was most often done without anesthetic and with only moderate discomfort to the patient. Posterior colpotomy was combined with examination under anesthetic with the patient prepared for laparotomy. Early in the series needle aspiration was infrequently used, but as more experience was gained in the use of this procedure fewer false negative results were obtained, and as a result it has been employed more often. Posterior colpotomy is not without risk of infection, but an analysis of the cases failed to reveal any such occurrence. Postoperative morbidity, wound infection, and stay in hospital were no greater in the cases of posterior colpotomy than all others. Many of the errors in diagnosis that were made could have been avoided if this procedure or aspiration had been employed more freely.

Diagnostic Errors

It was difficult to estimate fairly the number of diagnostic errors in these cases. Frequently ectopic pregnancy was suspected when the patient was first examined, but some other diagnosis was considered more probable, and the true nature of the case was recognized only after several days' observation in hospital. For the purpose of analysis, all cases in which a provisional diagnosis

of ectopic pregnancy was not made on initial examination were considered mistakes, even if ectopic pregnancy was considered. On this basis, 74 cases were erroneously diagnosed, an error of approximately 24 per cent. Observation in hospital, however, led to a correct preoperative diagnosis in 35 of these, leaving 39 cases, or slightly more than 10 per cent, in which a final diagnosis was incorrect. Chronic pelvic inflammation and various types of abortion were the most commonly made errors in diagnosis, the former being made 23 times and the latter 21 times. A diagnosis of a ruptured or twisted ovarian cyst was erroneously made 9 times and appendicitis 5 times. These errors in diagnosis led to needless prolongation of stay in hospital in many cases, a fatal termination in one case, and, in three others, severe internal hemorrhage occurred from which the patients recovered, but their lives were needlessly jeopardized. In every instance, ectopic pregnancy had been considered in the differential diagnosis, and if posterior colpotomy had been performed the mistake probably would have been avoided.

Many of the mistakes, even when reviewed, seemed justifiable. For example: three patients had acute gonorrhea with positive cervical smears, and two patients considering themselves to be pregnant, had attempted to induce an abortion by mechanical means. These are, however, the confusing facts that one encounters on a ward service that test the diagnostic acumen of the most astute.

Treatment

Treatment was aimed at the arrest of hemorrhage by suitable operative procedures and the replacement of blood volume by intravenous fluids, plasma, and blood transfusions. Early in the series, before a blood bank had been established at the hospital, laparotomy was frequently performed on patients in a state of shock who were receiving only intravenous saline. Eleven of these early patients received autotransfusion during operation, and 94 others received 500 c.c. or more of whole blood either during operation or in the immediate postoperative period. During recent years, since the establishment of a blood bank, autotransfusion has not been employed and blood transfusions have been used more freely. It may seem paradoxical to transfuse a patient who is still suffering from internal hemorrhage before that hemorrhage is arrested. Nevertheless, preoperative transfusions have been freely used and have resulted in the patient's reaching the operating room in an improved state to withstand the added shock of anesthetic and laparotomy.

The two most commonly employed operative procedures were salpingectomy in 150 cases, and salpingo-oophorectomy in 129 cases.

TABLE VI. OPERATIVE PROCEDURES, 302 CASES

Not operated upon	3 cases
Salpingectomy	150 cases
Salpingo-oophorectomy	129 cases
Hysterectomy with salpingectomy	14 cases
Bilateral salpingectomy	3 cases
Bilateral salpingo-oophorectomy	2 cases
Oophorectomy	1 case
Appendectomy	22 cases

On reviewing the pathological reports and sections, it was evident that in many of these 129 cases a healthy ovary had been needlessly sacrificed and simple salpingectomy should have been done. In 14 instances, hysterectomy was performed because of uterine fibroids. These patients were in the chronic group and the pathological description of the uterus appeared to justify the hysterectomy. In 22 cases appendectomy was performed, and while none of these patients

developed any postoperative complications, the hazard offered by appendectomy in the presence of blood in the peritoneal cavity is probably too great to warrant this procedure even in the chronic type of case.

Postoperative Complications

Serious postoperative complications were surprisingly few. There were three cases of subacute intestinal obstruction, none of which required surgical intervention. The commonest single postoperative complication involved the lungs; there were 11 cases with chest complications variously diagnosed as pleurisy, pneumonia, and atelectasis, with one case recognized as pulmonary embolus and deep femoral thrombosis. On reviewing these 11 cases in the light of present-day knowledge, it seems probable that many of them were unrecognized pulmonary emboli. It is interesting to note however, that none of these patients died, none received anticoagulant therapy, and in none was venous ligation performed.

Deaths

There were 7 deaths in the series, a mortality of 2.3 per cent. All deaths were due primarily to hemorrhage and shock, and surgical accidents played no role in any. Three patients died before operation. The first of these died one hour after admission to hospital before transfusion or operation was possible. In the second case a diagnosis of postabortal peritonitis was made and seemed justified on history and physical findings. Temperature was 101° F., respirations 33, and the abdomen was greatly distended. There was also a foul-smelling blood-stained vaginal discharge. This patient received three blood transfusions of 500 c.c. but lived only forty-eight hours and it was only shortly before death that ectopic pregnancy was suspected. The third patient was in hospital only two hours. On admission her general condition was excellent, there was no vaginal bleeding, and the patient's only complaint was lower abdominal pain. While the case was being considered by the house staff, rupture of the ectopic pregnancy occurred and the patient died twenty-two minutes later from internal hemorrhage.

The four remaining patients were all operated upon with a diagnosis of ectopic pregnancy, but delay in making the diagnosis was partly responsible for the fatal termination of one of these. An original diagnosis of acute pelvic inflammation was made. This was based on a temperature of 101° F., sedimentation rate of 15 minutes, and a pelvic mass. Twelve hours after admission the patient went into shock, and immediate operation was performed. A large intraligamentous hematoma added difficulty to the operation and despite three transfusions of 500 c.c. of whole blood, the patient never recovered from shock and died twelve hours later.

Two patients who received autotransfusions died. One died on the operating table from shock and the other on the tenth postoperative day from anuria. The remaining death occurred twelve hours after operation from shock. This patient received only a single 500 c.c. transfusion of whole blood and undoubtedly could have been saved by the freer use of transfusion.

Summary

A large number of cases of early extrauterine pregnancy have been reviewed. Included in the series were two cases of primary ovarian pregnancy and one case of chorionepithelioma of the tube. The incidence of ovarian pregnancy has been variously estimated from 0.7 to 1.0 per cent.[2, 3] It is probable, however, as suggested by Isbell and Bacon, that its frequency is greater than is generally

appreciated.[4] Chorionepithelioma, however, following ectopic pregnancy is a very rare occurrence.[5-8] The fact that the patient in this series recovered naturally raises doubts in regard to the correctness of the diagnosis, which, however, seemed justified on the microscopic characteristics of the lesion.

The relatively high initial diagnostic error of 24 per cent reflects the varied and often obscure clinical picture presented by ectopic pregnancy. A history of amenorrhea which is usually considered along with pain and bleeding as a cardinal symptom of tubal pregnancy occurred in only half the cases. A combination of a high white blood count, normal sedimentation rate, and a slight degree of fever was highly suggestive of blood in the peritoneal cavity. The most valuable aids in diagnosis were posterior colpotomy and aspiration of the cul-de-sac.[9] Decidual reaction in the endometrium was so infrequently observed that its absence could not be considered significant.

All the deaths resulted primarily from hemorrhage and shock. Diagnostic errors, delay in obtaining blood for transfusion, and the use of inadequate quantities of blood all played a role in these fatalities.

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Discussion

DR. FRANK E. WHITACRE, Memphis, Tenn.—Early extrauterine pregnancy is one of our most perplexing problems. The incidence of pelvic inflammatory disease in the Mid-South as seen in a general hospital is high; therefore the incidence of ectopic pregnancy is somewhat greater in our material than that reported by the authors. Since a previous report on ectopic pregnancy from our department, we have treated 61 cases in less than two years. The usual problem in differential diagnosis is to distinguish early ectopic pregnancy from uterine abortion. One-third of our patients had had no vaginal bleeding before rupture of an early tubal pregnancy, which agrees with the authors' conclusion that bleeding is often not a cardinal symptom of this condition. Of the remainder, all but two had had vaginal bleeding on or before the sixth week of gestation; whereas, the bleeding of uterine abortion is most common from the eighth to the twelfth weeks. This emphasizes the necessity of taking a careful history as to the onset of bleeding. Almost all of our patients had spotting of varying amounts which became dark in color as distinguished from the gush of bright red blood usually seen in uterine abortions. The tearing, stabbing type of pain was experienced by the majority of our patients at the time of rupture or tubal abortion, as distinguished from the cramplike, rhythmical contractions associated with uterine abortion.

Two years ago we reported the possibility that the detection of hemochromogen in the peripheral blood might be valuable as an aid to the diagnosis of bleeding into a body cavity. Mistakes have been infrequent with this test, but we have had a number of false negative reactions. It is possible that the state of vascular collapse of the patients interfered with the mechanism of absorption by the peritoneum of the breakdown products of hemoglobin. At any rate, more work must be done and perhaps changes made in the technique to make this test more reliable.

I commend Dr. Henderson especially for his insistence upon aspiration of the cul-de-sac in suspected cases. In general, our results in this small series of 61 cases agree with the findings at the Toronto General Hospital. Four additional patients were thought to have had an early ectopic pregnancy, but some other condition was found in three at operation. In the fourth case blood was obtained from the cul-de-sac aspiration, and neither ectopic pregnancy nor other gross pathology was demonstrable at operation. We can only presume that the needle entered a retroperitoneal vein or some other unusual occurrence took place, but this in no way nullifies the value of the procedure.

Of the 61 patients, practically all received intravenous fluids and blood transfusions before and during operation. No autotransfusions were given. At operation removal of the affected tube was the usual procedure, but the ovary on the affected side was removed in one-third of our cases, which is higher than it should be.

The signs and symptoms observed in our series agree almost exactly with those found by Dr. Henderson.

The only death in our series was that of a patient who died in vascular collapse five minutes after admission to the hospital and before treatment of any kind could be instituted. From the experiences of the author and our own, we feel that aspiration of the cul-de-sac of Douglas should be mandatory in suspected cases of ruptured ectopic pregnancy.

DR. JAMES W. KENNEDY, Philadelphia, Pa.—Practical experience is a very vital necessity in ectopic pregnancy. Rupture may lead to a rapidly fatal termination which is the greatest tragedy in the entire field of gynecology.

We feel it would be merciful and productive of better therapy if the young physician did not write on these potential tragedies until he has had twenty years of practical experience.

We feel the tender cervix is the most reliable of the physical signs, when it is properly elicited. The finger should be passed over the vaginal fornix with great gentleness from side to side; as the finger touches the cervix the patient winces or complains of pain. Remember that in ectopic pregnancy the cervix is more tender than the lateral mass of pyosalpinx and the reverse is true in the infected pelvis. The ectopic patient bears surgery better than any other similar shock patient. We would like to call attention to what we call the open circulation as of value in its relation to the pulseless patient. The patient often has no pulse. Within five or ten seconds, when we had tied or clamped the bleeding vessel, the pulse is easily perceptible at the wrist. We feel this open circulation has much to do with the collapse of the patient. Rarely, if ever, is there enough blood in the abdominal cavity incident to the ectopic pregnancy to account for the pulseless or dead patient. We never puncture the vaginal vault for diagnostic purposes.

It is difficult to reconcile the clinical and physical signs in ectopic pregnancy with the picture often seen. For instance, compare the picture seen in the acute ectopic patient with the postoperative hemorrhage in abdominal surgery. Hemorrhage exists in each case, yet we see here a paradox reaching its greatest possibilities in symptoms. The ectopic patient is the quiet, blanched, subdued, motionless patient; whereas, the patient with postoperative hemorrhage is the wild, thirsty, ever-moving, foot out of the bed, difficult-to-nurse patient. Yet each has intra-abdominal hemorrhage.

The acutely ill ectopic patient is always operated upon the first hour we see the patient. Time is precious. Do not delay for preoperative treatment of any kind. The greatest gentleness must be used in operative treatment of acute ectopic pregnancies.

DR. A. D. CAMPBELL, Montreal, Quebec.—I would like to warn against relying on a posterior colpotomy. An ectopic pregnancy may be present with no blood in the cul-de-sac. A colpotomy in such cases is not only valueless, but misinformative. Therefore, to rely upon colpotomy can be a dangerous diagnostic procedure.

DR. W. WAYNE BABCOCK, Philadelphia, Pa.—This very interesting paper and discussion lead me to question why the operator, having by vaginal puncture entered the

pelvis and made the diagnosis of ectopic pregnancy, does not at once proceed through the vaginal vault with the quickest and safest method of controlling tubal hemorrhage. Forty years ago the death of an exsanguinated patient turned me to the vaginal approach. In the vaginal operation the puncture is made by curved scissors, and the two index fingers are then introduced to spread the opening through the posterior vault. By touch, one immediately locates the enlarged tube, which, possibly with the added aid of a ring forceps, is brought down into the vagina and clamped, arresting all tubal hemorrhage. If the patient is in great shock, this, with the insertion of a gauze drain, may terminate the operation, or in the usual case one simply ligates and resects the tube or appendage and removes the clamp. Finally, a very important part of this simple three- to five-minute operation is the drainage of the pelvis. I push the center of a double layer of iodoform gauze, 12 inches square, through the vaginal wound into the pelvis, and then, aided by a narrow trowel, pack this with parallel strips of folded gauze, forming a Mikulicz drain. During the operation, performed largely by the sense of touch, one pays little attention to escaping blood or to its removal, as the peritoneum will gradually be cleared by drainage during the postoperative period. If you pull out the drain the day after operation, as I have had assistants do, you will probably be called to replace prolapsed coils of intestine. If you pull out the drain two to five days after operation, the opening in the vaginal vault will close, usually two soon, with rise in temperature and the necessity for reopening the vault by the gloved finger. If you merely withdraw one or two of the inner strips of gauze, beginning on the fifth and completing the gauze removal on the eighth day a smooth convalescence should follow. By leaving the gauze in long enough for it to loosen, complications are avoided. Five or eight minutes of anesthesia without special relaxation are required in the average case. Compare this with the intra-abdominal manipulations, time required, and anesthesia necessary for an abdominal section together with the unnecessary burden all this imposes on an exsanguinated patient.

DR. HENDERSON (Closing).—We have not employed Dr. Whitacre's test for hemochromogen in the serum, but it is certainly one that is worth investigating and the mere fact that there are false negatives would not mitigate against the usefulness of the test. Dr. Campbell's statement that with an unruptured ectopic pregnancy the posterior colpotomy will be negative, is quite true, but such cases are rare and full reliance should never be placed on any single diagnostic aid. The acute cases of ectopic pregnancy present no problem in diagnosis. It is the chronic case on the ward service where abortion may have been attempted which causes the greatest confusion in diagnosis. With aspiration in these cases we would have had fewer errors.

I did not have time to mention anything about the findings on pelvic examination. Pelvic tenderness is best elicited, as Dr. Kennedy outlined, by gentle palpation of the cervix. In one-fourth of the patients we could not feel a pelvic mass. With regard to vaginal operation for approach to ectopic pregnancy, I have had no experience. It certainly does not appeal to me, and difficulty with hemorrhage might be terrifying.

THE MANAGEMENT OF PLACENTA PREVIA*

A Review of 201 Cases With Emphasis on Conservatism

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THIS collective review is an extended study of the results obtained in the treatment of placenta previa at the Maternity Division of St. Joseph's Infirmary, Houston, Texas. The first study,[1] which was published in 1945, reviewed 79 cases occurring in 24,626 consecutive term or near-term deliveries. This review includes an additional 122 cases occurring in 25,374 deliveries or, in combination, 201 cases of placenta previa occurring in 50,000 consecutive term or near-term deliveries. The time covered is from Oct. 1, 1939, to Jan. 15, 1949, i.e., roughly ten years. Frequent reference to the first paper may be necessary as this presentation is a continued effort to support the contentions originally offered, namely: (1) that the inference in acceptable textbooks to the effect that even the first hemorrhage in a case of placenta previa may be fatal is too frightening and unwarranted; (2) that the teaching that pregnancy should be interrupted with the diagnosis of placenta previa is unjustifiable; (3) that the bleeding in placenta previa is intermittent and occurs only with dilatation of the cervix and/or lower uterine segment and separation of the placenta and not with each uterine contraction; (4) that by careful vaginal examination a reasonably accurate diagnosis of the three varieties of previa may be made; (5) that blood for replacement should be at hand in the treatment of all varieties; (6) that a safe time must be selected for those cases terminated by cesarean section; (7) that labor when strictly conservative should be conducted without any effort to hasten it; (8) that any remaining placental tissue after the second stage of labor should be allowed to separate naturally; and (9) that delivery by cesarean section or the strictly conservative method which was outlined in the first paper[1] offers the best fetal and maternal mortality as compared to other techniques involving manipulation (vaginal packs, bagging, version, etc.).

It is unnecessary to mention the reasons why vaginal, cervical, or intrauterine trauma upset the natural mechanism which protects the previa patient. This natural mechanism may also be upset when the placenta is, in addition, an accreta. In the first paper, it was contended that, if unmanipulated, the patient would not bleed to death because the blood loss is intermittent in character and occurs only when dilatation of the cervix or lower uterine segment causes placental separation and that this dilatation is not synchronous with each labor pain

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but occurs as a summation of several pains. Normal labor exhibits this periodicity of cervical dilatation and is more readily demonstrated in multiparas. The blood pressure may go down to shock levels during a severe bout of bleeding, but healthy capillary endothelium is ravenous in sucking serum into the blood stream, and, before the next bout of bleeding occurs, the blood volume is sufficient to cause the blood pressure to return to a safe level. This mechanism appeared so convincing that years ago I offered a reward for the report of any case where an unaccreted placenta previa, without manipulation, had caused a fatal hemorrhage. No awards have been made to date. The feeling that the patient will not bleed to death should give one a great deal of assurance, but, at the same time, failure to become alarmed and resort to untimely intervention does not always meet with sympathetic acceptance by many colleagues and the hospital personnel in general. There is another source of comfort.

No textbook fails to mention the name of William Smellie[2] in the chapter on placenta previa. He is considered the "granddaddy" of all English-speaking obstetricians. For its reassuring effect I will quote from him: "On the first appearance of flooding, the patient ought immediately to be blooded to the amount of eight or twelve ounces, and venae-section repeated occasionally according to the strength of the constitution and emergency of the case. She ought to be confined to her bed, and be rather cool than warm. If costive, an emollient glyster must be injected in order to dissolve the hardened faeces, that they may be expelled easily without straining, etc."

In reverence, and as much as one might like to agree with this obstetrical saint, present-day obstetrics is not in accord with his treatment. It shows, however, that Smellie did not share the rather general present-day alarm over blood loss in these patients and frequently thought that the amount lost might be inadequate.

The insistence that pregnancy should be terminated as soon as placenta previa is diagnosed is no longer defensible. Such teaching reached the status of an obstetrical dictum when maternal mortality rates were far different from those of today. The textbooks are fast relegating this concept to obstetrical history and are stressing the details of safe management of the previa patient so that she may be carried to good viability of the fetus. Happily, the complete disregard for this early teaching has enabled the writer to accumulate a few good friends who, without such disregard, would not be living today. A canvas of these persons would no doubt show them to be congenitally opposed to the "dictum." Many of the patients in this series were hospitalized or made repeated visits to the hospital for blood studies while awaiting better fetal viability.

The first paper expressed the opinion that rectal examinations are contraindicated in the bleeding obstetrical patient and that the diagnosis of placenta previa must still depend largely on vaginal examination by trained fingers. If facilities for x-ray confirmation are at hand, they should by all means be taken advantage of, but the number of cases of previa compared to the number of trained soft-tissue roentgenologists is most disproportionate. Time may remedy this condition. Without suggesting that vaginal examinations replace rectal examinations in routine obstetrics, the contention is now made that in the train-

ing of an obstetrician a sufficient number (hundreds) of sterile vaginal examinations should be made in varying stages of the last trimester or near term. In my opinion, these examinations would not be hazardous to the patient and would serve to impress and better orient one with the pelvic findings in a normal case so that departures from the normal might be more readily detected.

With the present prejudice against vaginal examination anywhere or any time, it might be suggested that the term be changed to "vaginal palpation." Such palpation enables the trained fingers to palpate in normal cases the entire lower hemisphere of the presenting pole through the lower uterine segment and above the internal os. In feeling posteriorly the forearm should not be parallel to the patient's body, but the elbow must be depressed as in measuring the internal conjugate diameter. If the presenting pole cannot be palpated, one is immediately in the realm of abnormal obstetrics—presenting part at or above the inlet, a variety of placenta previa, transverse or oblique presentation, pelvic neoplasm, abdominal pregnancy, fundal incarceration, polyhydramnios, etc. A central placenta previa is quickly detected, but, in the suspected partial or marginal varieties, the palpation continues in search of intervening tissue and, if found, its extent and its location with reference to the internal os are noted. We advise that the cervical canal not be invaded except in a multipara at or near term or when in labor and then only for the purpose of rupturing the membranes. Vaginal palpation may be coincident with a bout of bleeding, but, unless it is rough enough to cause dilatation and separation, it will not produce hemorrhage. It goes without saying that, because of the tendency of previa patients to develop infection, strict precautions must be taken while making this diagnostic vaginal palpation.

The criticism might be made that the term "lower uterine segment" is used too freely and perhaps without the proper understanding of its meaning. The writer appreciates the three rather distinct concepts concerning this portion of the uterus: (1) that it is an anatomical and functional entity which forms during labor; (2) that it is a segment of the uterus which is, during the last trimester of pregnancy, accommodating one-third of the crown-rump dimension of the fetus and extends from the then present ledge or physiological ring to the internal os, and does become slightly thinner during labor; and (3) the most recent delineation by Danforth and Ivy,[3] which in substance describes the lower uterine segment as that portion of the lower part of the uterus which surrounds the largest circumference of the presenting pole and extends downward to the internal os and which must dilate to permit the passage of the fetus. Because of the writer's interest in contraction-ring dystocia, preference is had for the second concept. But, regardless of the foregoing, there is a thin-walled portion of the uterus above the internal os through which in normal cases the presenting pole may be palpated.

The benefit of replacement of blood where labor is conducted conservatively is obvious. But it must be realized that many full-time and more part-time obstetricians have not this advantage. They should feel that as beneficial as is blood replacement, it still is not an absolute requirement in the conservative treat-

ment. However, it should be deemed a vital necessity in cases treated by cesarean section, and every section undertaken without adequate blood at hand carries an unwarranted risk to the patient.

Bill[4] was among the first to point out that cesarean section should not be undertaken unless the blood pressure was at a safe level, and he regarded a systolic pressure of 90 as the minimum. This was before the days of available blood and its proper matching, so his rule might now, in certain cases, be judiciously broken. Nevertheless, a disregard of this rule is attended by great danger. A few obstetricians working at St. Joseph's Hospital say that they just cannot stand to see the patient bleed to death, and in four cases of the last series, cesarean section was started when the blood pressure was at or within shock levels. One cannot brag over a maternal mortality of *nil* when here alone were four potential deaths.

The blood loss in conservative management is greatly decreased if the membranes are ruptured artificially and they should be ruptured as early in labor as possible. This decrease in blood loss may be due (1) to the fetal head coming down and acting as a tampon during periods of uterine contractions; (2) to the reducing of the intrauterine volume, which may give abrupted sinuses a better chance to be occluded by myometrial retraction; and (3) to the stopping of the pull, if there be such, of the membranes on that part of the placenta which is being separated. It would seem that small doses of Pituitrin to hasten the labor would be distinctly contraindicated. The longer the intervals between the pains, the longer will be the intervals of dilatation and separation with their consequent bleeding. The fetal mortality in this series might have been lower if amniotomy had been done in more cases.

Students fail to see the sense in our teaching that in the presence of free bleeding placental tissue should be *manually removed* from the *body of the non-previa uterus,* but should be allowed to remain and *separate naturally* during the third stage *in cases of placenta previa.* Unopened sinuses in such instances are not bleeding, and the whole theme in placenta previa is to make blood loss as gradual and minimal as possible. When tissue is removed from the body of the uterus, the latter immediately exercises that facility which it has of contracting and retracting. In the lower uterine segment, this facility is greatly decreased and its failure to retract promptly causes, when the sinuses are abruptly opened, a quick and excessive loss of blood.

While abdominal surgery appears to offer a very low fetal mortality, there is at least one factor which will bear further investigation. Curiosity caused a close scrutiny of the last fifteen sections with reference to fetal and infant welfare. A study was made of the condition of the baby at operation, and during his stay in the nursery as noted on the charts. There were two fetal deaths; one baby expired shortly after delivery and another expired during the operation. Of the remaining thirteen, examination of the charts showed evidence of intracranial damage in six. In most cases the damage seemed to warrant the assumption of some mental retardation later in life. The question of asphyxial hemorrhage should be further investigated in all methods of delivery.

As stated in a previous paper,[1] the staff at St. Joseph's is heterogeneous but fairly well controlled by an organized consultation system. In checking this last series it was found that in practically all instances the patients were attended or treatment guided by a so-called obstetrical specialist. The definition of an obstetrical specialist, for purposes of this paper, has been liberalized to include seasoned obstetricians, with all diplomates of the American Board, and those with most excellent formal or basic training but with very meager experience in abnormal obstetrics.

The incidence of placenta previa in this series was found to be one in every 250 deliveries at or near term (Stander, 1 in 206). This low rate is a compliment either to the vigor of the trophoblast or the endometrial unimpoverishment in the Houston area.

In the last series of 122 cases of previa, the records did not indicate the parity in two instances. Twenty-nine, or 24 per cent, of the remaining 120 cases occurred in primiparas. The 91 multiparas had had 285 pregnancies, an average of 3.1 each, and one of these accounted for 13 pregnancies.

As expected, the maternal morbidity in these cases was high. Thirty, or 24.5 per cent, of them had morbid puerperia. Further breakdown reveals that 17 morbid puerperia followed cesarean section, i.e., in one-third of those delivered abdominally while the corresponding figure for vaginal delivery was only 18.3 per cent.

Many of these cases were not carried to term, the average gestational period for the series being 35 weeks. Incidence of variety of placenta previa for the previous and the current series is shown in Table I. Diagnosis as to variety was made at the time of delivery and this information was obtained from the delivery or operative records.

TABLE I. INCIDENCE OF VARIOUS TYPES OF PLACENTA PREVIA

SERIES	NO. OF CASES	VARIETY					
		CENTRALIS		PARTIALIS		MARGINALIS	
		NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
I	79	26	33	15	19	38	48
II	122	31	24	21	17	70	57
I and II	201	57	28	36	18	108	54
Stander	—	—	36	—	18	—	44

Method of delivery and fetal mortality rates for each are shown in Table II. The first series permits of a corrected fetal mortality of 22.2 per cent, but the writer feels that uncorrected mortalities are more significant. so seven cases under seven calendar months, two macerated fetuses, and one monster were reincorporated to give an uncorrected mortality of 30.1 per cent. The apparent discrepancy in fetal mortality between the first and second series is no doubt due to poor indexing and the inclusion in the first series of some cases of late abortion. In its earlier years, the hospital's records were inferior to their present state. Also, there appears to be a decided improvement in the fetal mortality rate of the second series in both the section and conservative methods.

Two cesarean sections were followed by hysterectomy because of placenta previa accreta. A third case of accreta has occurred since the series closed January 15. In this last instance the placenta was accreted over only a small area and an attempt was made to save the uterus because of the age of the patient. Repeated bouts of bleeding necessitated a total hysterectomy twelve days after

cesarean section. Because of the absence of the spongiosa layer in the decidua of the lower uterine segment, it seems strange that more previas are not accreted.

Fifty patients of the last series were given 117 units or pints of blood, an average of 2.3 pints of blood per patient. As stated before, the maternal mortality was nil, no patient having bled to death, but a near fatality occurred when, paradoxically enough, the bleeding was thrown into reverse. A diligent resident with some basic training, knowing the value of a lot of blood and intravenous fluids, kept both going. Timely bloodletting by an internist relieved the acute congestive failure.

There was one case reported with central placenta previa associated with severe pre-eclampsia (blood pressure 140/100) and death of fetus from erythroblastosis fetalis following cesarean section. The diagnosis might be questioned as severe pre-eclampsia and placenta previa are seldom found in the same patient.

There were three sets of twins in the first series and none in the last. Two patients reported in the first series had repeat previas and therefore appear again in the last series.

In conclusion the writer wishes to offer no criticism of the so-called "double setup" which is so commonly used in the various clinics in the treatment of placenta previa. However, he cannot avoid the feeling that the assembling of so much obstetrical talent and material is somewhat disproportionate to the gravity of the situation. To overemphasize this point, it is recalled that recently at St. Joseph's a perfect "double setup" was in readiness. Anxiety and tension pervaded this grave situation fraught with so many possibilities. Imagine the great relief which came over all the talent, and possibly the material, when it was found that the bleeding was coming from a mole on the labia majora.

TABLE IIA. METHOD OF DELIVERY AND FETAL MORTALITY IN EACH (UNCORRECTED). FIRST SERIES

METHOD OF DELIVERY	CASES NO.	DEATHS NO.	FETUSES NO.	MORTALITY PER CENT
Cesarean section	42	10	43 (1 twin)	23.2
Strictly conservative	29	9	31 (2 twins)	29.1
Other techniques	8	6	9 (1 twin)	66.7
Total	79	25	83	30.1

TABLE IIB. METHOD OF DELIVERY AND FETAL MORTALITY IN EACH (UNCORRECTED). SECOND SERIES

METHOD OF DELIVERY	CASES NO.	DEATHS NO.	FETUSES NO.	MORTALITY %
Cesarean section	51	4	51	8.0
Strictly conservative	66	11	66	16.0
Other techniques	5	3	5	60.0
Total	122	18	122	14.7
Total, both series	201	43	205	21.0

Summary and Conclusions

1. The management of 201 consecutive cases of placenta previa at a large maternity hospital with a heterogeneous staff is reviewed.

2. Attention is called to the conclusions arrived at in an earlier and similar review of a smaller series.

3. Unmanipulated cases of placenta previa will not bleed to death because the blood loss from this condition is intermittent and in each interim the patient has ample time to recover spontaneously from the resultant shock.

4. Fetal salvage can be increased through careful evaluation of the case by blood studies after each bout of bleeding and through carrying the pregnancy to more certain fetal viability.

5. Careful vaginal examination by trained fingers continues to be the most accurate means of diagnosis of placenta previa. Rectal examinations are contraindicated in the bleeding obstetrical patient.

6. Training of each obstetrician should include a large number of sterile vaginal examinations in the last trimester of pregnancy.

7. Trained fingers can diagnose placenta previa, even its different varieties, without invading the uterine cavity. They will not precipitate hemorrhage.

8. Blood should be available for all cases of previa, more particularly for those delivered abdominally.

9. Cesarean section for placenta previa must not be undertaken with a patient in shock.

10. Conservative management of this condition calls for rupture of membranes as early in labor as possible.

11. Placental tissue should not be manually removed in cases of previa. This is contrary to the management of such tissue retained from a normally implanted placenta.

12. While delivery by cesarean section suggests a lower infant loss than per vaginal delivery, there is reason to suspect fetal damage with the former which may not be obvious until months or years later.

13. Seventy-six per cent of the patients were multiparas with the average number of pregnancies in these being 3.1.

14. The maternal morbidity for the series was 24.5 per cent, with one-third of them delivered by cesarean section, but was only 18.3 per cent for those delivered vaginally.

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TOPOGRAPHIC URETHROGRAPHY*

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Part I

THE surgery of urinary incontinence in women is noted for its high percentage of failures. It would help immeasurably if the anatomical result were known in the successful cases as well as in the failures. Then the surgeon should be able to satisfy himself at the operating table that he has restored the anatomy to conditions compatible with continence. It is folly to expect the same operation to cure a slender patient with a shallow symphysis as well as a very obese patient with a deep symphysis; to cure stress incontinence, a result of parturition, as well as the congenital cases with spina bifida; to cure a patient without respiratory disease as well as patients with chronic coughs due to asthma and bronchiectasis. If the sutures in a plication of the bladder neck are placed in a routine fashion on all types of patients without regard to what is to be accomplished in a particular case, it will result in a goodly share of failures. In this study a method has been developed which demonstrates the position of the bladder neck in relation to the inferior border of the symphysis. It has been used successfully in the diagnosis, preoperative planning, and prognosis in a wide variety of patients with incontinence. In practice it places the surgery of this condition on a sound anatomical basis and leaves little to chance.

Topography of the Symphysis.—

The medial surfaces of the pubic bones have certain features which may be more or less well defined in different subjects.[1] These features depend on age, pregnancies, and arthritic changes, in addition to inherited bony features of the pelvis (Fig. 1). The symphyseal face has a dorsal and ventral margin and a lower and upper extremity. Extending from the dorsal margin for some distance over the face one may occasionally discern an area outlined by virtue of a condensation of the bone of the articular surface. This is called the dorsal platform. Near the upper extremity an upper nodule or epiphysis may be evident and very rarely a lower nodule is seen. The bone between these two nodules, making up the remainder of the symphyseal face is called the ventral rampart. While these landmarks may not be all present or distinct even in dried pelves some one or other feature can usually be seen. By searching for these features, which fortunately become more distinct after the third decade, a quite accurate outline of the symphysis may be obtained.

The symphysis is seen in a right lateral view with both symphyseal facies, the adjacent portions of the superior and inferior rami, and the pubic tubercles contributing to the densities seen on x-ray (Figs. 4, 5, 6). While the features

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described as seen in dried pelves cannot be seen as such on the x-ray they may aid in locating certain densities. What appear to be the upper nodules together with the pubic tubercles can be seen. The condensations formed by the development of rims and lipping most frequently stand out. The anterior and posterior borders become rimmed in the older age groups and are not difficult to outline. Occasionally a condensation is evident in the inferior portion of the symphysis which is interpreted as representing the lower nodule. In the older age groups there may be marked lipping in some parts of the borders while some areas show rarefaction. A satisfactory outline of the symphysis is possible if the technical detail of the film is reasonably good.

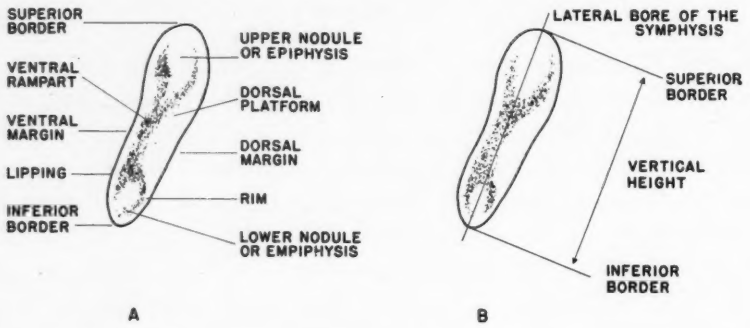

Fig. 1.—Semidiagrammatic representations of the right symphyseal face. A. Composite picture of various features some of which may be present. B. Lines showing the lateral bore of the symphysis and method of measuring its vertical height.

The distance between the superior and inferior borders of the symphysis along a line drawn through the middle of the symphyseal face represents the vertical height of the symphysis (Fig. 1, B). The superior border is the upper edge of the pubic tubercles as seen in this projection. This may be a few millimeters higher or at the same level as a rim indicating the superior edge of the upper nodule in the midline. The inferior border of the symphysis is the lower edge of the symphysis from which there falls away the ridge to which the arcuate ligament is attached or the lower margin of a rim when this is present. The average vertical height of the symphysis in 105 women studied was 4.7 cm. The range of measurements was 3.9 to 5.6 cm.

The inferior border is more difficult to locate in the absence of a definite rim to make it visible. The following method was devised for this purpose. Lines are drawn along the anterior and posterior margins of the symphysis as far inferiorly as they can be traced. Lines are drawn along the anterior and posterior margins of both inferior pubic rami as far superiorly as they can be traced. The lines of the symphysis and the lines of the rami tend to turn slightly posterior as they approach each other. The average level at which the lines superiorly and inferiorly intersect is taken as the inferior border of the symphysis.

The lateral bore of the symphysis used in this method is defined as a vertical line drawn through the middle of the symphyseal face and representing the general slope of the symphysis (Fig. 1, B). The line is drawn through the maximum number of mid-points in the symphyseal face since this will result in a line representing the general slope of the structure in relation to other bony landmarks. Where there are pronounced pubic tubercles at the anterosuperior border, this density is not included in the bisection. It is evident that this line provides a fixed landmark regardless of the position, attitude, or rotation of the patient in a sagittal plane.

The Technique of the Urethrograms.—

There now remains to indicate by some method the external meatus and the bladder neck, or, as it is more commonly called, the internal sphincter. A No. 18 Foley catheter with a 30 c.c. capacity bag was modified for this purpose (Fig. 2). A sheath of 30 Fr. in diameter was added and the end of the catheter sealed. A metal marker with an internal diameter of 26 Fr. is used to mark the external meatus. The bladder is filled with 250 c.c. of 5 per cent sodium

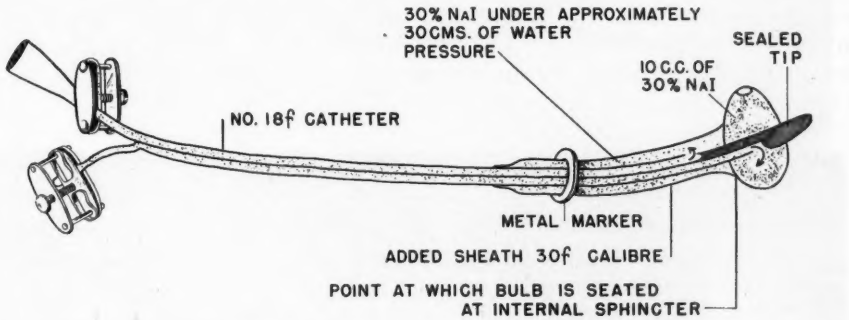

Fig. 2.—Diagram of special catheter with tip sealed and added sheath. The metal marker may be moved along the sheath as required by the length of the urethra and the position of the external meatus.

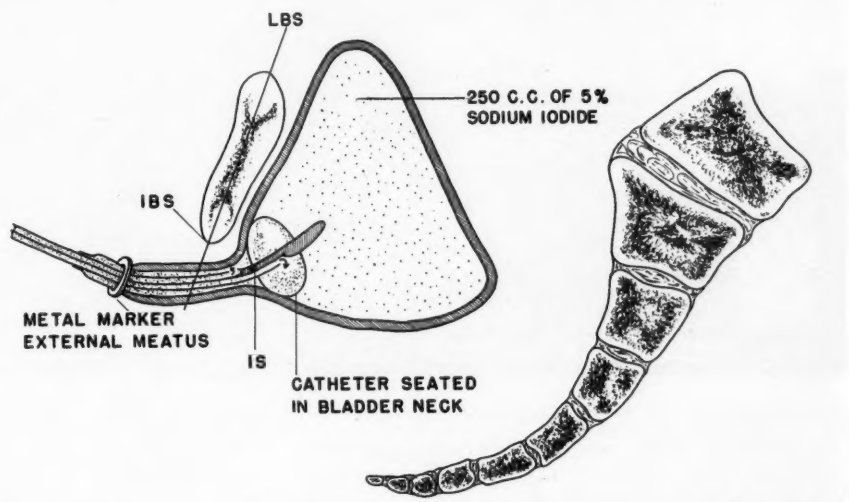

Fig. 3.—Composite diagram showing the special catheter in position, the lateral bore of the symphysis, and the landmarks used in a true lateral cystourethrogram to measure the position of the bladder neck.

iodide in each case and the measurements therefore represent conditions in a full bladder. The catheter is inserted and both bulb and sheath inflated with 30 per cent sodium iodide for contrast (Fig. 3). The sheath of each catheter used is calibrated by a simple water manometer for the amount that will give approximately a pressure of 30 cm. of water.[2] This is the pressure a normal urethra can close against and while not part of this study it was felt this factor should be constant in all patients. The metal marker is now adjusted so the bulb is seated in the bladder neck. Being fixed at two points the catheter remains undisturbed throughout the tests.

Any technique that gives a true lateral isometric x-ray of the pelvis may now be used.[3] Studies are done in the sitting position with the back 30 degrees above the horizontal and in the standing position. In each position plates are taken at rest, with the patient attempting to void, and with the patient attempting to hold back the urinary stream. It is appreciated that the patient is attempting to void against resistance and closed urethra. However, with an empty bladder the urethra and particularly the bladder neck swing in an arc under the symphysis on voluntary attempts to void. The presence of the catheter may cause a slight error but the factors are constant throughout all the tests in any patient and collectively for all the patients studied. Studies of the physiology of micturition by voiding cystourethrograms corroborate this but do not permit exact measurements.[4]

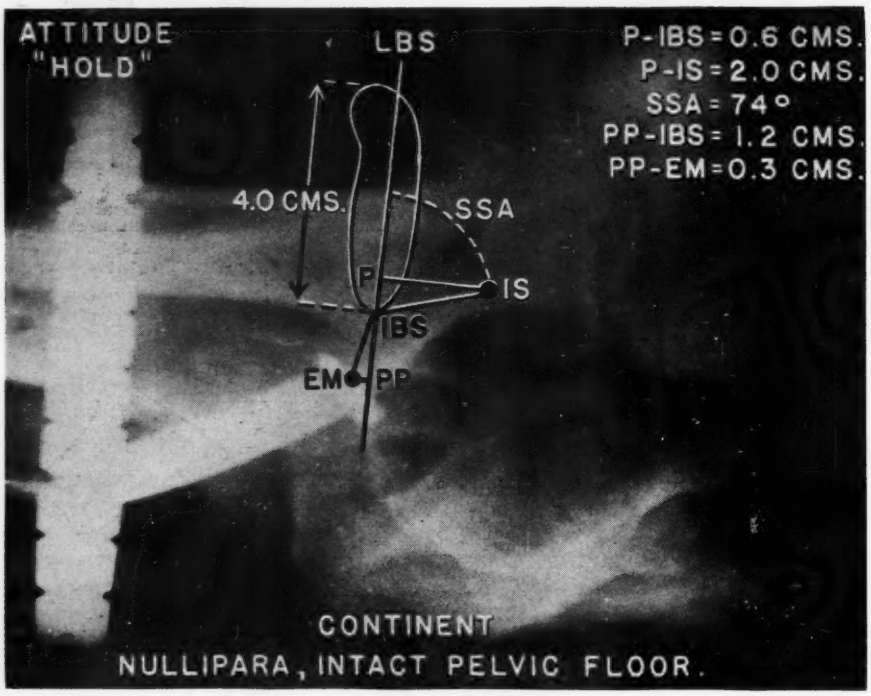

Fig. 4.—Number 36442, nullipara with intact pelvic floor. In the sitting position, "hold" attitude, the bladder neck is drawn up well behind the symphysis. The external meatus is only 3 mm. anterior to the lateral bore of the symphysis.

Interpretation of the X-rays.—

The bladder neck and external meatus are located in reference to the lateral bore and inferior border of the symphysis. The outline of the symphysis and other measurements are made with a wax pencil on the x-ray plate. Figs. 4, 5, and 6 show a nullipara in the sitting position and hold, rest, and strain attitudes. The metal centimeter ruler in lateral projection allows distances to be measured directly. A line is drawn from the bladder neck, IS, to the inferior border of the symphysis. A second line, P-IS, is a perpendicular from the bladder neck to the lateral bore of the symphysis. The external meatus, EM, is triangulated in the same manner and the angle SSA measured. The bladder neck and external meatus are located by measuring the distances they are anterior or posterior to the lateral bore of the symphysis and the distances they are superior or inferior to its inferior border measured along its lateral bore. In Fig. 7

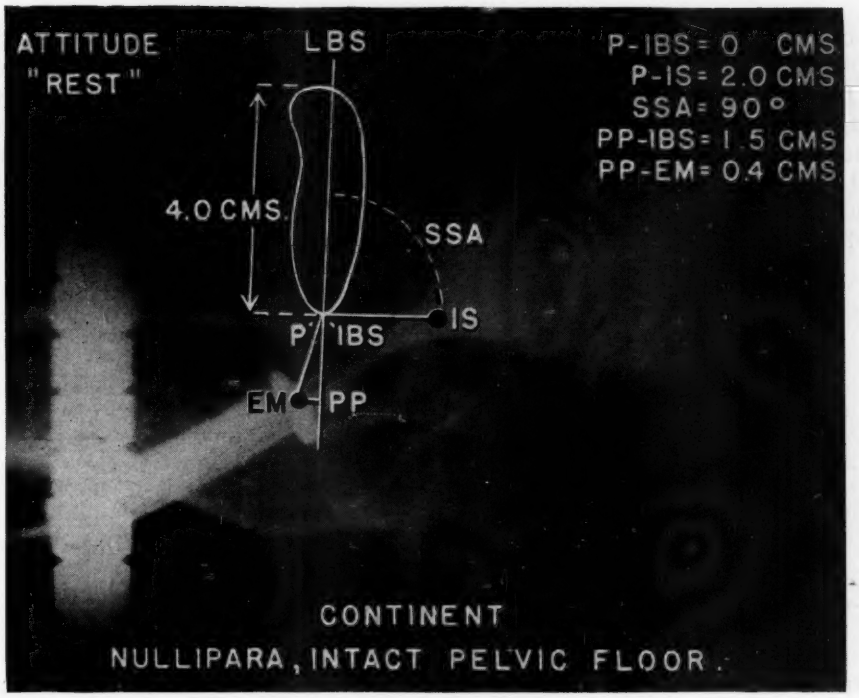

Fig. 5.—The same patient as in Fig. 4 in the "rest" attitude. The bladder neck rests on the same plane as the inferior border of the symphysis. The external meatus moved very slightly downward and forward.

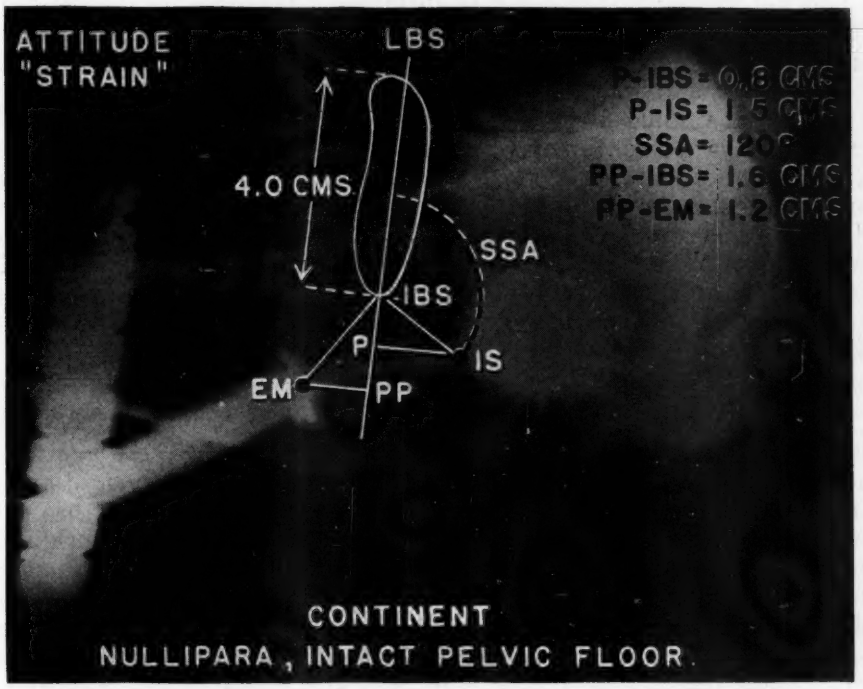

Fig. 6.—The same patient as in Figs. 4 and 5 in the "strain" attitude. The bladder neck moves downward 0.8 cm. and forward 0.5 cm. from the "rest" film. The external meatus moves forward 0.8 cm. but only 1 mm. downward. The bladder neck remains well behind the symphysis.

these distances would be P-IS, P-IBS, PP-EM and PP-IBS. The line LBS-IBS-IS forms the sphincterosymphyseal angle. This method allows the patient to move between films, to sit or stand, and still permits accurate measurements since the fixed points of reference remain constant. The angle SSA roughly reflects the movement of the bladder neck about the symphysis in the various positions and attitudes. A similar angle can be measured for the external meatus but the movement here is more limited and does not add a great deal to the interpretation of the plates.

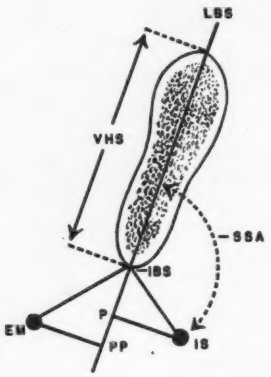

Fig. 7.—Method of measuring distances by simple triangulation. LBS, lateral bore of the symphysis; P, PP, points along LBS; IS, the bladder neck; EM, external meatus; SSA, sphincterosymphyseal angle; VHS, vertical height of the symphysis.

It must be emphasized from the start that the interpretation must be functional and not simply a measuring of distances. However, to discuss the findings it is necessary to show the average values for continent females seen in Tables I and II. The patients studied included nulliparas, multiparas with slight relaxation, and multiparas with relaxation and prolapse. Most of the latter group had vaginal hysterectomies or a Manchester type repair after these tests. They were all continent. The average values as determined for these patients would not stand statistical analysis. They do not show the range of motion or the extremes among patients of the three groups. These will be discussed later. We can say from the averages that there is a tendency in the group as a whole to displace the bladder neck and external meatus to such and such a distance and draw some practical conclusions from this phase of the study. The x-rays incidentally are also examined for bony lesions of the pelvis and bladder diverticuli and polyps that might show in this projection.

The Position of the External Meatus.—

The distance of the external meatus anterior to the lateral bore of the symphysis in the three groups shows no great difference. There is a tendency for the meatus to be further anterior after parturition. The position in the hold, rest, and strain attitudes indicates that the external meatus has a range of movement from 0.6 to 0.8 cm., taking the averages for the group in the sitting position. From the rest position it moves forward about 0.5 cm. during micturition. In the standing position the meatus starts out more anterior to the lateral bore and moves forward a few millimeters less while voiding. Study of Figs. 4, 5, and 6 shows the movements of an individual patient in the sitting position. These plates compared side by side give a functional picture of what happens in the various attitudes and mean more than comparisons of averages for a group. Space would not permit the material to be presented as individual cases.

TABLE I. SITTING POSITION

	ATTITUDE	CONTINENT NULLIPARAS	CONTINENT MULTIPARAS WITH SLIGHT RELAXATION	CONTINENT MULTIPARAS WITH RELAXATION AND PROLAPSE
Number of patients studied		10	11	6
Average distance of EM anterior to LBS (PP-EM)	Hold	1.0*	1.1	1.3
	Rest	1.3	1.3	1.5
	Strain	1.8	1.7	1.9
Average distance of EM inferior to IBS (PP-IBS)	Hold	1.3	1.7	1.5
	Rest	1.3	1.7	1.7
	Strain	1.3	1.7	1.5
Average distance of IS posterior to LBS (P-IS)	Hold	2.1	1.9	1.6
	Rest	1.8	1.8	1.6
	Strain	1.5	1.6	1.4
Average distance of IS inferior to IBS (P-IBS)	Hold	0.7†	0.4†	0.2†
	Rest	0.4†	0.1†	0.1†
	Strain	0.3	0.5	0.6
Average sphincterosymphyseal angle (SSA)	Hold	71 degrees	79 degrees	90 degrees
	Rest	80 degrees	86 degrees	96 degrees
	Strain	103 degrees	105 degrees	117 degrees

*Distances are measured in centimeters.
†This distance is measured superior to IBS.

TABLE II. STANDING POSITION

	ATTITUDE	CONTINENT NULLIPARAS	CONTINENT MULTIPARAS WITH SLIGHT RELAXATION	CONTINENT MULTIPARAS WITH RELAXATION AND PROLAPSE
Number of patients studied		10	11	6
Average distance of EM anterior to LBS (PP-EM)	Hold	1.8*	1.7	2.3
	Rest	1.8	1.7	2.1
	Strain	2.2	2.0	2.6
Average distance of EM inferior to IBS (PP-IBS)	Hold	1.2	1.7	1.6
	Rest	1.4	1.7	1.8
	Strain	1.5	1.8	1.5
Average distance of IS posterior to LBS (P-IS)	Hold	1.6	1.8	1.1
	Rest	1.6	1.9	1.0
	Strain	1.3	1.3	0.8
Average distance of IS inferior to IBS (P-IBS)	Hold	0.4†	0.4	0.7
	Rest	0.1†	0.7	0.9
	Strain	0.8	1.7	1.2
Average sphincterosymphyseal angle (SSA)	Hold	78 degrees	104 degrees	102 degrees
	Rest	89 degrees	109 degrees	131 degrees
	Strain	121 degrees	140 degrees	144 degrees

*Distances are measured in centimeters.
†This distance is measured superior to IBS.

The Position of theBladder Neck.—

The external meatus has a tendency to be more inferior to the inferior border of the symphysis after parturition. There is not a great deal of difference between the sitting and standing positions. When averages are used multiparas with slight relaxation have their external meati at a slightly lower level than patients with prolapse. It is possible that atrophic changes may account for this in the older patients of the prolapse group.

The position of the bladder neck is the focal point of the study. The terms bladder neck or bladder isthmus are preferable to the term internal sphincter

because of the difference of opinion as to the existence of a circular sphincter as such. However, because of common usage we have continued the use of the term but use it interchangeably with bladder neck. In the sitting position, rest attitude, it is noted that the sphincter is 1.8 cm. behind the lateral bore of the symphysis as an average among the continent nulliparas studied. It is slightly more anterior after parturition. It moves forward a few millimeters on attempts to void. This is less marked by a small margin in the multiparas studied. The point is that the bladder neck does not move forward an appreciable distance in continent females. When a woman with relaxation and prolapse is continent, the relaxation of the vaginal wall is posterior to the bladder neck and the paraurethral supports are good. It would appear that in this type of pelvic floor relaxation the pubococcygeus is intact, possibly sheared off from the rest of the levator ani, and continues to hold the bladder neck in a favorable position for the maintenance of urinary continence. In the standing position the bladder neck is normally more forward in relation to the lateral bore.

The bladder neck ranges from positions superior to and inferior to a plane perpendicular to the lateral bore at the inferior border of the symphysis (Fig. 7, P-IBS). Again, it is at a lower level after childbirth and in the standing position. In the standing position there is a significant difference in the level at which the bladder neck is found in nulliparas and multiparas. The sphincterosymphyseal angle reflects in general the above changes in the location of the bladder neck in the various patients, positions, and attitudes. However, mathematically it is not significant at all since the bladder neck could be anywhere along the line IS-IBS and the angle remain constant. It helps somewhat in that it roughly indicates the arc along which the bladder neck is displaced from the rest position in the hold and strain attitudes.

There are many variations in position and range of movement when individual patients are studied. To average corresponding measurements in a group of patients only gives a baseline for interpretation of an individual case. For example, consider the movement forward of the internal sphincter when two different patients strain down. In the first the internal sphincter starts out 2.0 cm. behind the lateral bore and in the second it is 1.2 cm. In the latter patient a movement forward of 0.5 cm. displaces the sphincter out of the range usually seen in normal or continent patients; i.e., to a point only 0.7 cm. posterior to the lateral bore. In the former patient who starts out with the bladder neck well behind the symphysis this is not the case. Thus it is evident that in the interpretation of the films no critical angles or critical distances can be set down which delineate sharply one case from another in regard to continence. The position at rest, the direction of movement on straining, the distance moved collectively give a functional picture that is useful in evaluating the patient. A patient may have measurements all of which conform within a few millimeters to the group average except one measurement that is at the extreme. In general, the distances are within 3 mm. on either side of the group average with the occasional measurement outside this range. With this individual variation among similar cases it is quite evident that the averages shown in the tables where differences of only 1 or 2 mm. exist indicate only a tendency to be in a certain position and not exact measurements. In later parts of the study where patients with severe stress incontinence are encountered there are significant differences in the measurements showing displacement of the bladder neck.

This paper deals with the technique of topographic urethrography and the normal findings. From a practical point of view the method is used to study stress incontinence in women, to analyze operative failures, suggest individual variations needed in the operative correction of incontinence, and help distinguish between true stress incontinence and the urgency-frequency dribbling of

posterior urethritis. To this end later communications deal with the abnormal cases. The technique is simplified for practical use and only the standing position need be used as this is the most significant in true stress incontinence.

Summary and Conclusions

1. A method called "topographic urethrography" is introduced as a means of studying the geometric relation of the urethra to the symphysis pubis in continent and incontinent women.

2. The technique and results of a study of twenty-seven normal women are reported.

3. Following parturition there is a tendency for the urethra to be slightly more anterior and inferior to the symphysis than in the nulliparous woman.

4. Continent women with relaxation and prolapse show good paraurethral support as evidenced by the position of the urethra in the urethrograms. The relaxation of the vaginal wall in these patients is posterior to the bladder neck.

5. In the standing position the urethra has a tendency to occupy a position more anterior and inferior to the symphysis than in the sitting position.

6. The method has practical applications in the study and management of patients with primary and recurrent stress incontinence. The x-rays may suggest variations from the standard techniques that are necessary at operation for a successful outcome. They may help distinguish between true stress incontinence and the urgency-frequency dribbling of posterior urethritis. These are the subjects of later reports.

The author is indebted to Mrs. Jessie Lockhart, x-ray technician to the Woman's Clinic, who patiently instructed the patients before and during the taking of the films.

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TOPOGRAPHIC URETHROGRAPHY

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Part II

The Mechanism of Stress Incontinence.—

Stress incontinence is accompanied by a displacement of the bladder neck in an arc forward and somewhat downward from its normal position in relation to the inferior border of the symphysis. The forward displacement is the significant factor and from this an accordion effect results in the inner third of the urethra. This same area is funneled when viewed from inside and a sluggish, gaping, internal orifice is seen through the water urethroscope. To close this bladder neck there is too much to be "taken up." Even with forceful voluntary efforts such displaced and funneled bladder isthmi fail to give a prompt response.

A normally placed, unimpaired bladder neck with intact paraurethral attachments has an action, when viewed directly, comparable to that seen at either end of the popular Chinese love trap toy seen in Fig. 1. It is not clear what is the exact muscular mechanism that gives this action. Dislocation and distortion of the inner third of the urethra make it impossible to close this portion of the bladder neck and urethra as do normal patients. While it is hard to grade the degree of incontinence either by history or demonstration, the results of this study would indicate that the incompetence of the bladder isthmus is roughly proportional to its displacement and funneling. Our thinking would be more realistic if we would think in terms of the dislocation of the bladder neck rather than the size of a cystocele or urethrocele.

The Incontinent Multipara With Slight Relaxation.—

Many patients with severe incontinence show only a minimal relaxation of the anterior vaginal wall. Nevertheless there is poor paraurethral support as shown by this method. The physical examination is not impressive if one looks only for the presence or absence of a urethrocele. This study has shown that it is not possible to determine the position of the bladder neck with accuracy by vaginal examination alone. Its location determined by the examiner is frequently very different from its true location demonstrated by x-ray.

Tables I and II show the results obtained by this method in twenty incontinent multiparas with slight relaxation of the anterior vaginal wall. By slight relaxation is meant a parous vagina that would be considered as showing good support. Their primary complaint was incontinence. Comparing this group to the continent multiparas who have the same degree of relaxation or even to the continent multiparas with large cystoceles and prolapse is very revealing. First, the external meatus in the rest attitude is further anterior to the lateral bore of the symphysis. It reflects the abnormal mobility of the urethra by moving an average distance of 2.6 cm. anterior to the lateral bore.

Attention is again called to the fact that these are averages and are used only to show what the tendency is in the group as a whole. The external meatus does not rest significantly lower in relation to the symphysis in the incontinent women. It does move in a significant manner in the strain attitude. As seen in the table it moves upward to an average level of 1.2 cm. below IBS. This supports the well-known observation that a glass catheter placed in the urethra

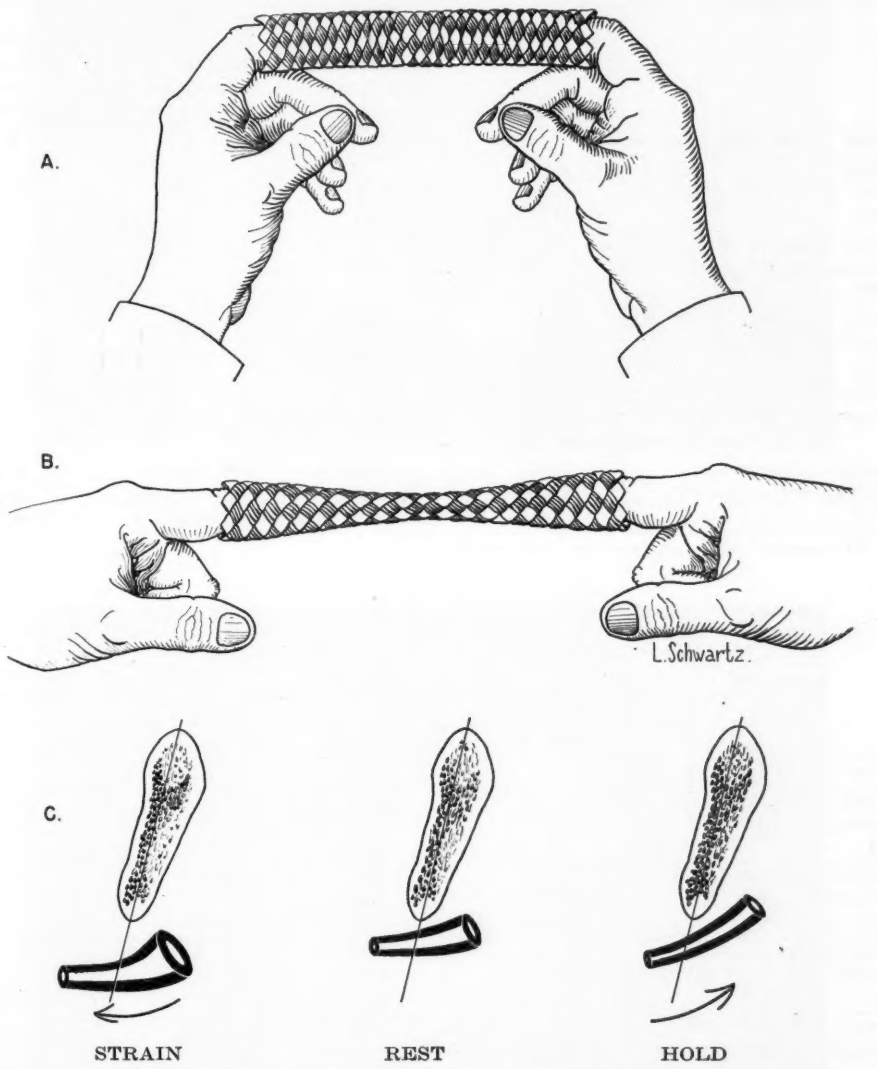

Fig. 1.—Closure of the bladder neck by movements similar to that seen at one end of the familiar Chinese love trap toy. Water urethroscopy and topographic urethrography demonstrated the mechanism.

in the dorsal lithotomy position turns upward forming a more obtuse angle with the horizontal when the patient strains down. This movement is exaggerated in the incontinent subjects as can be seen in the tables. It is realized that the metal marker is displaced somewhat away from the external meatus during the strain film. This makes the forward motion of the external meatus slightly more than it actually is. Since the same error occurs with the normal patients studied, it is valid to interpret the abnormal by comparison. This was such a

noticeable feature of the incontinent women as to direct considerable attention to the external meatus and its mobility during the physical examination of these patients. While the distal two-thirds of the urethra is not felt to be important in obtaining a competent bladder neck it seems to reflect the displacement and mobility of the latter so as to be quite informative.

TABLE I. SITTING POSITION

	ATTITUDE	INCONTINENT MULTIPARAS WITH SLIGHT RELAXATION	INCONTINENT MULTIPARAS WITH RELAXATION AND PROLAPSE	NULLIPARAS WITH CONGENITAL INCONTINENCE
Number of patients studied		20	7	6
Average distance of EM anterior to LBS (PP-EM)	Hold	1.5*	1.5	1.8
	Rest	1.6	1.8	1.9
	Strain	2.6	2.7	2.9
Average distance of EM inferior to IBS (PP-IBS)	Hold	1.6	1.5	1.7
	Rest	1.6	1.3	1.8
	Strain	1.2	0.5	0.1
Average distance of IS posterior to LBS (P-IS)	Hold	1.8	1.4	1.4
	Rest	1.8	1.1	1.2
	Strain	0.8	0.0	0.3
Average distance of IS inferior to IBS (P-IBS)	Hold	0.1	0.5	0.4
	Rest	0.3	0.6	0.8
	Strain	1.4	1.4	1.3
Average sphincterosymphyseal angle (SSA)	Hold	93 degrees	106 degrees	113 degrees
	Rest	98 degrees	124 degrees	122 degrees
	Strain	142 degrees	172 degrees	156 degrees

*Distances are measured in centimeters.

TABLE II. STANDING POSITION

	ATTITUDE	INCONTINENT MULTIPARAS WITH SLIGHT RELAXATION	INCONTINENT MULTIPARAS WITH RELAXATION AND PROLAPSE	NULLIPARAS WITH CONGENITAL INCONTINENCE
Number of patients studied		20	7	6
Average distance of EM anterior to LBS (PP-EM)	Hold	2.4*	2.2	1.6
	Rest	2.2	2.7	2.5
	Strain	2.8	2.6	3.3
Average distance of EM inferior to IBS (PP-IBS)	Hold	1.4	1.3	1.2
	Rest	1.5	0.9	1.5
	Strain	1.3	0.6	0.8
Average distance of IS posterior to LBS (P-IS)	Hold	1.1	0.2†	0.8
	Rest	1.2	0.3†	1.0
	Strain	0.3	1.0†	0.1†
Average distance of IS inferior to IBS (P-IBS)	Hold	0.9	1.4	1.0
	Rest	0.9	1.5	1.1
	Strain	1.9	1.7	1.6
Average sphincterosymphyseal angle (SSA)	Hold	128 degrees	181 degrees	138 degrees
	Rest	127 degrees	188 degrees	132 degrees
	Strain	166 degrees	214 degrees	177 degrees

*Distances are measured in centimeters.
†Indicates distances anterior to LBS.

The bladder neck as measured by this method rested 1.8 cm. behind the lateral bore of the symphysis in the rest attitude among the patients studied. They were not able to draw it much more posterior by voluntary efforts. The

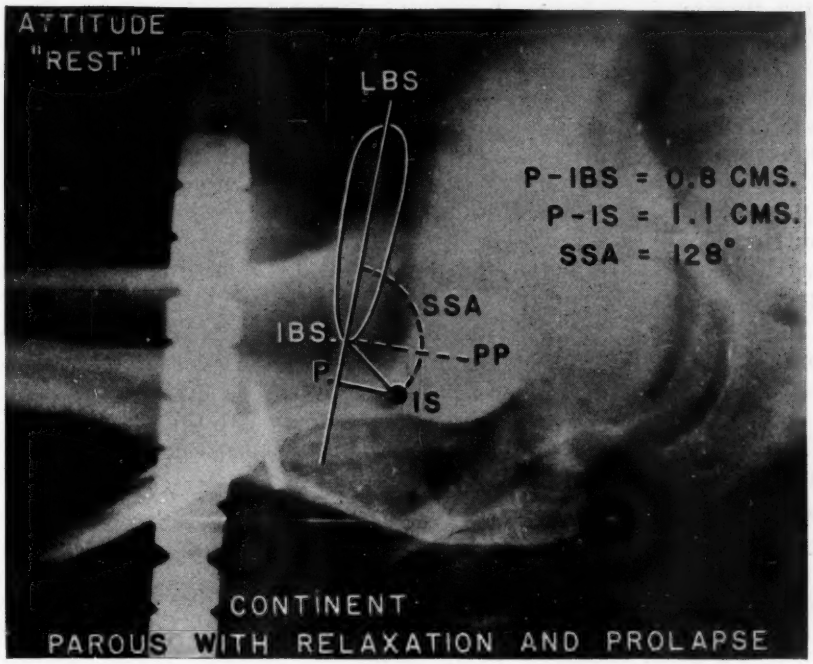

Fig. 2.—Number 521301, para v, gravida viii, twins i, with moderately large cystocele and rectocele. Descensus of cervix to outlet. In the sitting position, attitude, "rest," the bladder neck (IS) retains a good position posterior to the lateral bore of the symphysis (LBS). Continent.

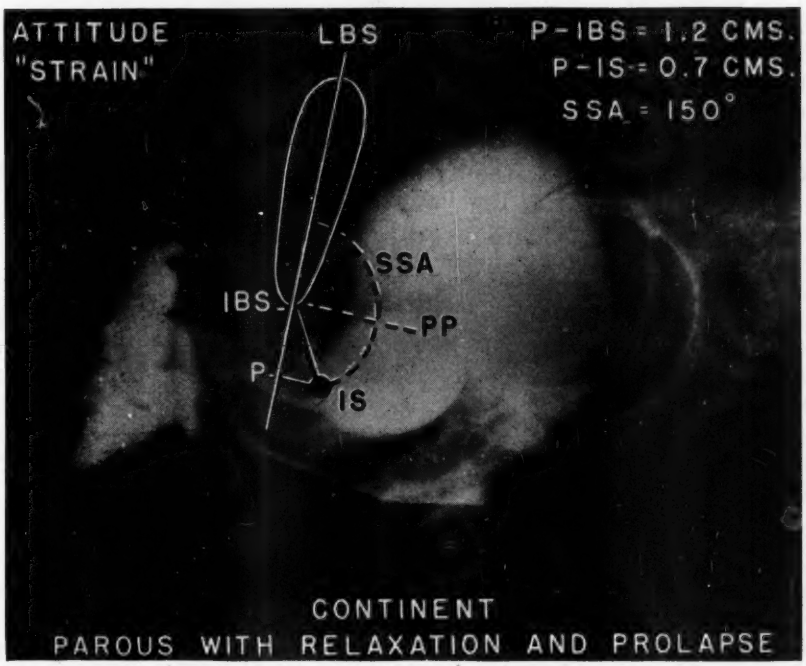

Fig. 3.—Same patient as in Fig. 2 in the sitting position, attitude, "strain." While the bladder neck (IS) moved forward 0.4 cm. from the "rest" attitude, it still remains well behind the lateral bore (LBS). Continent.

significant finding is a forward movement of 1.0 cm. in the strain attitude. It is this abnormal mobility particularly to a position less far behind the lateral bore of the symphysis that is seen among incontinent women and not seen among nulliparas or parous women with complete urinary control. The bladder neck rests at a lower level in relation to the inferior border of the symphysis in the group as a whole. In the strain attitude it moves to a level 1.4 cm. below IBS. The sphincterosymphyseal angles are larger than in the continent patients and roughly reflect the abnormal mobility. The downward motion probably contributes somewhat to the funneling of the bladder neck but is overshadowed by the importance of the forward component of the movement when individual x-rays are interpreted from a functional point of view.

In the standing position the external meatus tends to be more anterior to the lateral bore than in the sitting position. On the average it rests nearer to the plane of the inferior border of the symphysis as might be expected from gravity alone. The bladder neck lies closer to the lateral bore and at a lower level. The angles are larger in all attitudes. The sitting versus the standing position will be fully discussed later in the study.

The Incontinent Multipara With Relaxation and Prolapse.—

When a markedly relaxed outlet exists with poor paraurethral support the position and mobility of the urethra show a striking difference from that of the continent patient. The abnormal mobility is more marked than in the incontinent multipara with slight relaxation. The abnormal movements, however, are in the same direction. It is difficult to imagine the bladder neck so far forward, but it comes to rest, on an average, in the strain attitude, sitting position, at the lateral bore of the symphysis. Figs. 2, 3, 4, and 5 show the difference between a continent multipara with prolapse and one who is incontinent with the same degree of prolapse but with poor paraurethral support. The direction of movement and the mobility can be studied and compared in these patients. Among the continent multiparas with prolapse who were studied, the patient represented in Figs. 2 and 3 had the greatest mobility and displacement of the bladder neck. Yet, comparing her with one of the incontinent multiparas with prolapse, the bladder neck remains well behind the lateral bore in the strain attitude.

In the standing position the displacement is even more marked. Here the bladder neck rests anterior to the lateral bore of the symphysis in all three attitudes when the group is taken as a whole. From this abnormal position it is displaced even further. No patient who was x-rayed and continent showed anything like this except in complete procidentia where other factors obtain. That the bladder neck does rest so close to the lateral bore and even in front of it in some of these patients is of importance in placing the sutures in a plastic procedure for incontinence. It is possible that the plication is often done much posterior to the actual bladder neck in cases of operative failure. The distance of the bladder neck posterior to the symphysis or from the external meatus can be measured with very little error by this technique and the placing of the sutures done by actual measurement at the operating table.

Congenital Incontinence and Relaxation.—

The nulliparas with congenital incontinence and relaxation show a displacement of the urethra identical to that seen as a result of parturition. The average figures indicate some difference in that the congenitally relaxed nullipara tends to start out in the rest or hold attitudes in a more normal position but undergoes wide excursions in the strain attitude. This is not true for the individual case illustrated in Figs. 6 and 7. This patient not only started out with an exceedingly poor relationship in the rest attitude but also had further

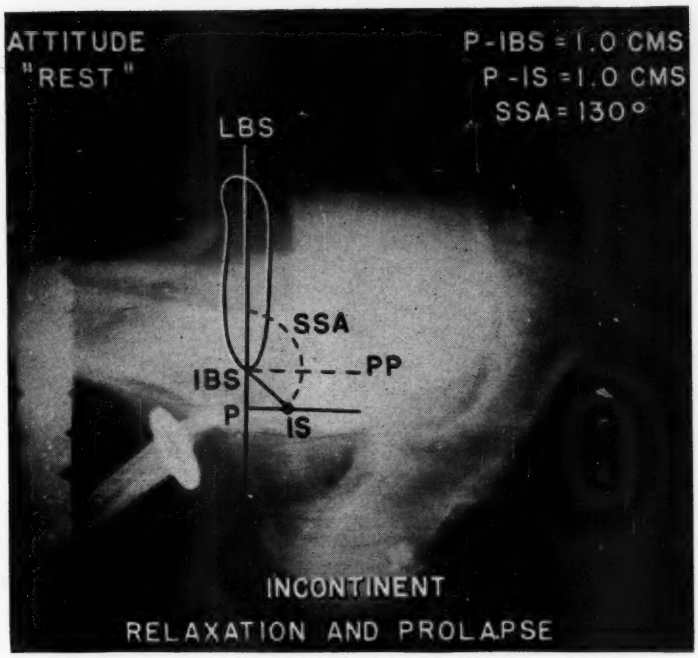

Fig. 4.—Number 516950, para ii, gravida iii, with moderately large cystocele and rectocele. Descensus of cervix to outlet. In the sitting position, attitude, "rest," the bladder neck (IS) has relatively good position behind the lateral bore of the symphysis (LBS). Incontinent.

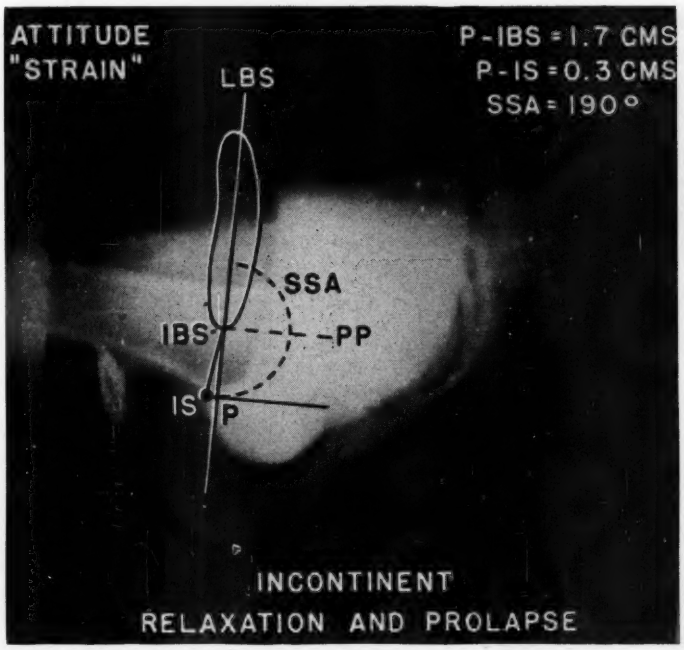

Fig. 5.—Same patient as in Fig. 4 in the sitting position, attitude, "strain." The bladder neck (IS) is displaced anterior to the lateral bore (LBS) showing abnormal mobility and poor paraurethral attachments. Incontinent.

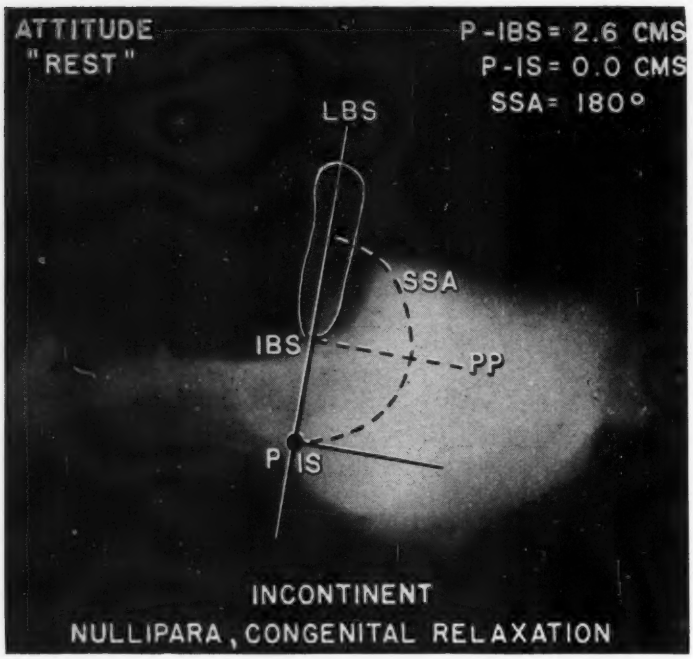

Fig. 6.—Number 196778, para 0, gravida 0, with moderately large cystocele. No rectocele or descensus. In the sitting position, attitude, "rest," the bladder neck (IS) is in a very poor position and rests in the same plane as the lateral bore of the symphysis (LBS). Incontinent.

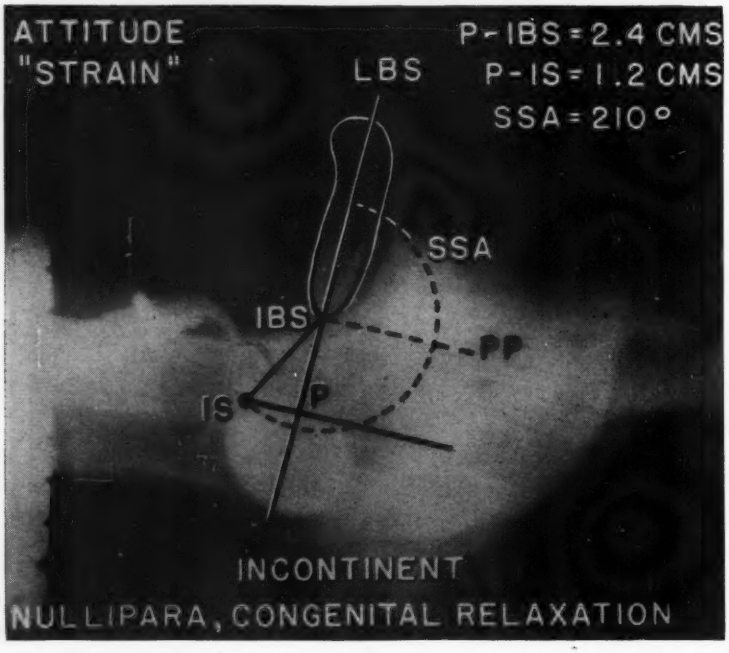

Fig. 7.—Same patient as in Fig. 6 in the sitting position, attitude, "strain." The bladder neck (IS) is 1.2 cm. in front of the lateral bore (LBS) indicating abnormal mobility and poor paraurethral attachments. Incontinent.

mobility in the strain attitude which displaced the bladder neck far anterior to the lateral bore of the symphysis. Turning again to Tables I and II, it is evident that the defect is even further exaggerated in the standing position.

In the six patients studied in this category, it was not possible to demonstrate a higher incidence of spina bifida or other neurological lesions. It is proposed that congenital incontinence is associated with some oddity of the puborectalis and anterior portions of the pubococcygeus. The outlets of these patients appear to be more caudad than usual as if the entire pelvic support were suspended at a lower level. Whether the levator ani is a longer and possibly more attenuated and underdeveloped muscle, or whether it arises along a line of origin more caudad than normally it is not possible to say. These studies would seem to indicate some such defect.

Summary and Conclusions

1. Stress incontinence is associated with a displacement of the bladder neck in an arc forward and downward in relation to the symphysis. This results in an accordion effect on the inner third of the urethra and a funneling of the bladder neck. The forward movement is the most significant.

2. Incontinent multiparas with slight relaxation and incontinent multiparas with relaxation and prolapse both show abnormal mobility of the bladder neck particularly in an anterior direction.

3. The sutures in a plication of the bladder neck may be very accurately placed in patients who have been x-rayed by this method. With the position and measurements known, a sterile tape or ruler may be used to measure from the external meatus or inferior border of the symphysis to the bladder neck. The error would probably be within a few millimeters.

4. After plication of the bladder neck, the distance to its new position can be measured at the operating table to see if it now rests in a position usually compatible with a competent bladder neck as demonstrated by these cystourethrograms.

5. Patients with congenital incontinence demonstrate the same defects as those resulting from parturition. It is proposed that a more caudad line of origin or an unusually elongated and attenuated levator sling is associated with congenital relaxation and incontinence.

STRESS INCONTINENCE OF URINE WITH SPECIAL REFERENCE TO FAILURE OF CURE FOLLOWING VAGINAL OPERATIVE PROCEDURE*

The Joseph Price Oration

CHARLES D. READ, M.B., F.R.C.S.E., F.R.A.C.S., F.R.C.O.G.
LONDON, ENGLAND

FAILURE to cure stress incontinence by the vaginal approach is the result of failure to achieve adequate elevation and fixation of the bladder neck, in the vast majority of cases I believe it can be accepted now that the main mechanism of bladder control resides in the region of the bladder neck, and that mobility and descent of the bladder neck on straining constitute the main factors which influence control. I hold the belief that the urethra per se has little influence. Much of the urethra may be excised without subsequent incontinence, and in several instances I have observed that the production of operative urethral strictures have failed to influence lack of control. Indeed, in the Couvelaire operation, control is attained entirely by the musculature of the trigone alone. I must express admiration for the work done in this field by American workers, the late Howard Kelly and Te Linde of Baltimore, Kennedy, Davis, Aldridge, and Studdiford of New York, Meigs and Muellner of Boston, and Counseller of the Mayo Clinic. The work of Kennedy undoubtedly led to a better appreciation of the factors involved in urinary control and stimulated many to a further study of the subject.

My colleague Terence Millin evolved further radiological investigations by observing the bladder neck in the resting and in the straining positions and a comparison of cystograms taken in both positions confirms Bonney's original contention that the essential lesion is a bladder neck descent on straining. We, together, published this work in the *Post-Graduate Medical Journal* in January-February, 1948. These observations were confirmed and published, with slight modifications in technique, a year later, by Muellner of Boston.

Failure to achieve cure by operative means almost invariably indicates failure to effect elevation and fixation of the bladder neck as shown in Figs. 5 and 6.

The two figures when compared with those preceding show for practical purposes little change and the patient still exhibits lack of control.

When cure of incontinence has been accomplished by the vaginal approach the cystographic appearances show a striking change as evidenced by Fig. 7.

*Presented, by invitation, at the Sixtieth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 8, 9, and 10, 1949.

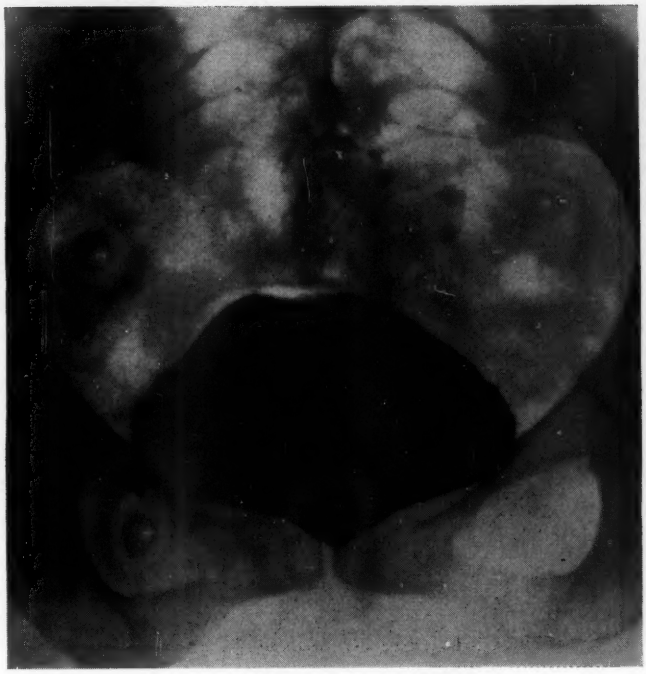

Fig. 1.—Normal resting position.

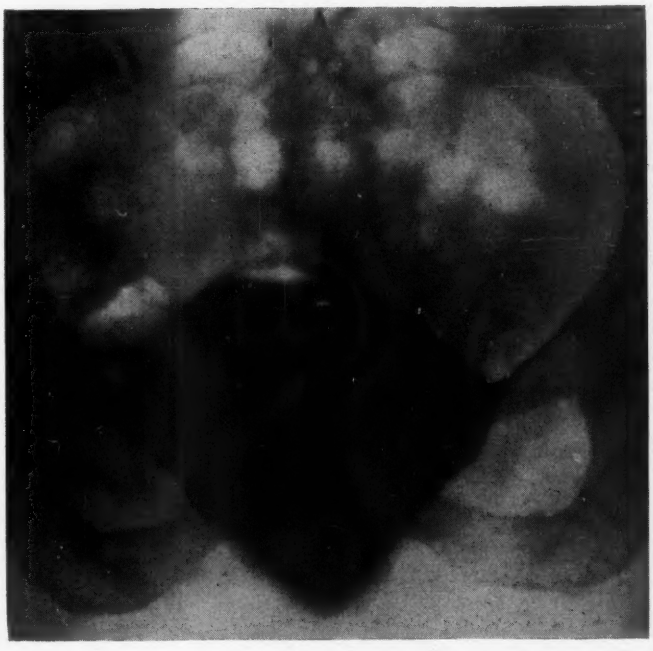

Fig. 2.—Straining position.

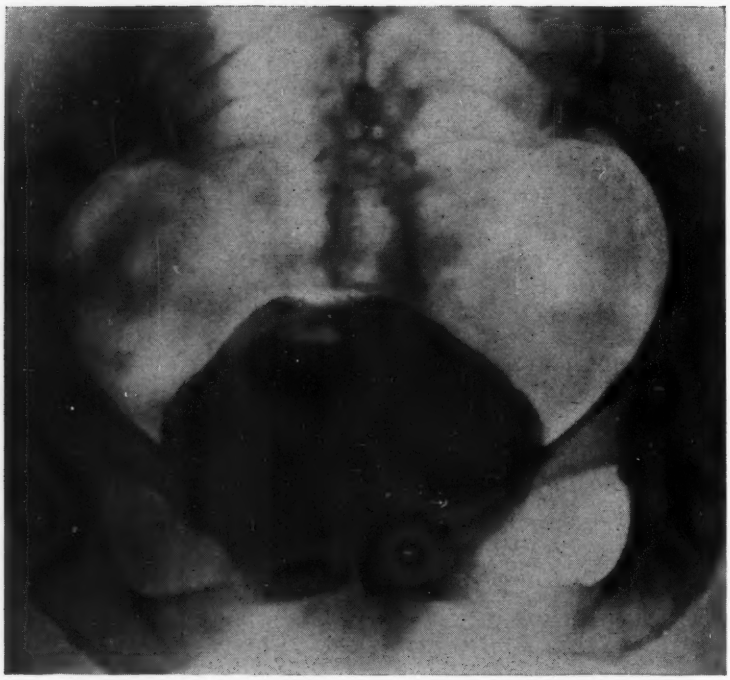

Fig. 3.—Superimposed Figs. 1 and 2, showing bladder neck descent.

Fig. 4.—Double exposure cystogram showing bladder neck descent.

Fig. 5.—Superimposed cystogram.

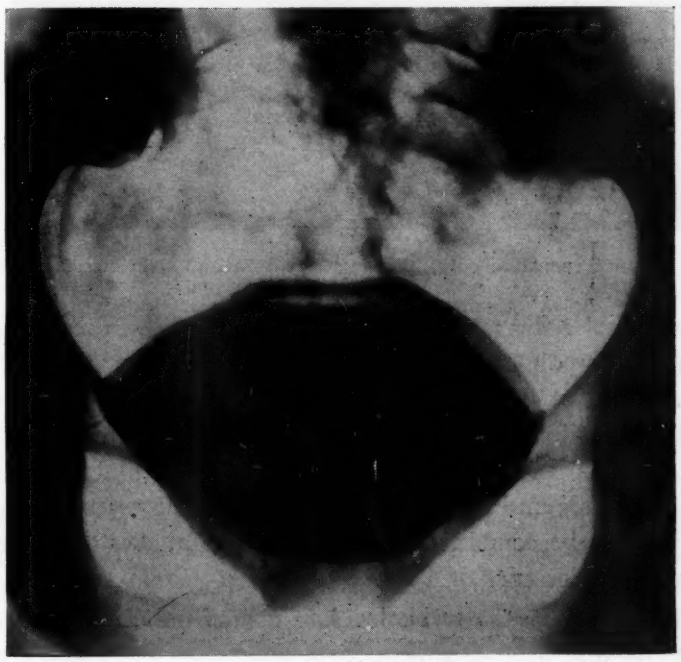

Fig. 6.—Before operation.

This cure was effected by an extensive vaginal procedure which involved through mobilization of the urethra, bladder neck, and bladder base, a wide lateral freeing of the vagina and bladder, a careful fascial repair and the firm approximation of the medial borders of the pubococcygeus muscles as described by Pacey. I have long come to the conclusion that no simple minor vaginal repair will cure any but the mildest degrees of orthostatic incontinence and the

Fig. 7.—After vaginal operative cure, showing elevation and fixation of the bladder neck.

surgeon who simply "takes a tuck" in the urethra and so-called vesical sphincter will have many disappointments. As with the treatment of urinary fistulas, the first vaginal attempt at cure should be the successful one—mobilization should be adequate, tension eliminated, sepsis avoided, and hematoma formation reduced to an absolute minimum. I have found the Pacey vaginal operation the most successful in my hands and Figs. 8, 9, and 10 show the essential features of the operation which can be combined with the usual Manchester operation for the cure of uterovaginal descent.

Ingleman-Sundberg of Stockholm has still further mobilized the pubococcygeus muscles and after dividing them he crosses them and fixes each portion of muscle with its nerve supply intact to the cervix on the opposite side. This is followed by a bulbocavernosus muscle approximation. He reports excellent results after a careful follow-up.

Various figures for the cure rate by the vaginal approach have been published by different observers. Te Linde has shown a 95 per cent cure rate and Kennedy shows figures approximating these. Counseller considers that these cure rates will show a falling off when the cases are subsequently investigated and this is the experience of Millin and myself, and we believe that, over all, about 75 per cent of patients are permanently cured. This admittedly allows for many inadequately performed operations. My recent experience suggests

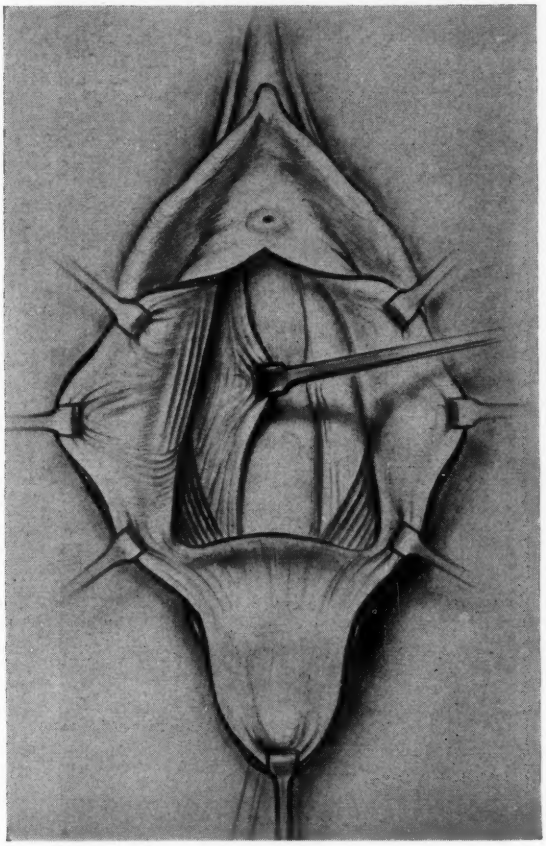

Fig. 8.—Vagina incised. Pubocervical fascia incised with edge shown grasped with Allis forceps. On left side of picture, corrugations of medial aspect of patient's right pubococcygeus muscle is shown.

that 90 per cent of patients will be cured if operative treatment be adequately executed by the vaginal route. There will remain a residuum of about 10 per cent of patients whose cure by the vaginal approach would appear to be impossible. These constitute a very interesting group and will include many patients showing a perfect result so far as cure of uterovaginal descent is concerned, and even some in whom incontinence has developed for the first time after successful repair of a prolapse. Technical errors, sepsis, and hematoma formation may be the factors involved, but whatever the cause of failure, the vast majority of such patients will show cystographically a bladder-neck descent in straining.

Here I must mention the ingenious perineometer of Kegel of Los Angeles. I have used the instrument on five patients, and can claim success in three of the five.

The use of the instrument will certainly not cure all stress incontinent patients, but it is especially efficacious in the recently postpartum woman. It is worth a trial in every patient who suffers from the disability without exhibiting

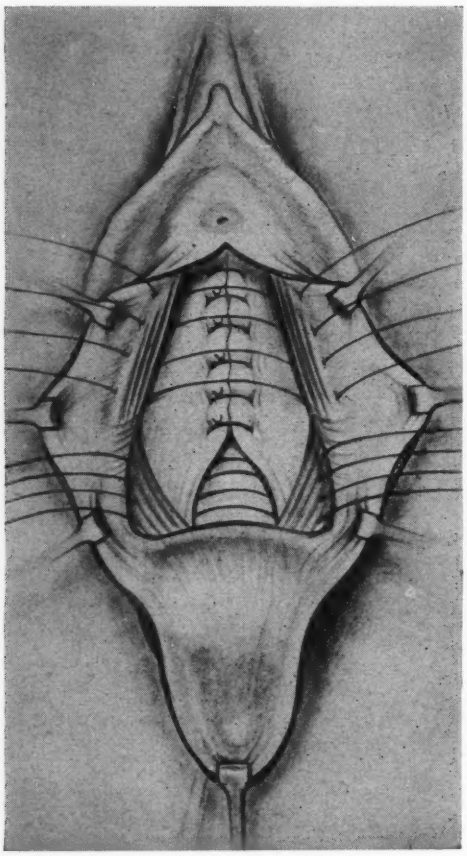

Fig. 9.—Pubocervical fascia approximated and sutures inserted through medial borders of pubococcygeus muscles.

marked uterovaginal descent, and it has a definite place in the treatment of the so-called relaxed pelvic diaphragm. Its use is simple, and the patients will cooperate well, and it certainly will appreciably diminish the necessity for operative treatment in such cases. In postmenopausal patients, the administration of estrogens in association with the use of the perineometer should prove helpful.

The multiplicity of operative procedures for the cure of these failures suggests that no one operation is completely successful in all cases. No group of patients is more miserable and pessimistic and no group is more grateful when subsequent cure is effected.

In the so-called failures, the choice of procedure lies between a repeat attempt via the vagina, and some more extensive procedure either by the abdominal route or by the combined abdominovaginal approach. Several of my patients have had four to seven vaginal attempts. One has had nine and one twelve such attempts. My practice has been to abandon the vaginal route when I have convinced myself that a reasonably adequate repair has previously been effected without cure.

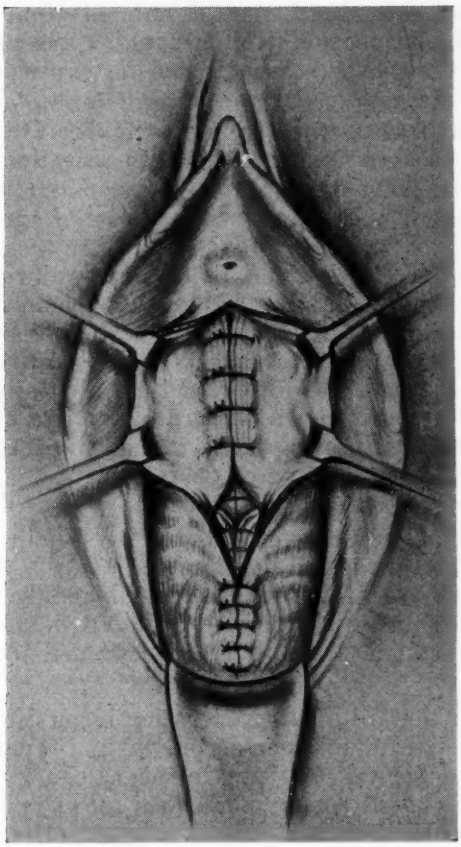

Fig. 10.—Pubococcygeus muscle edges approximated.

It cannot be too strongly emphasized that the more radical procedures about to be described are justifiable only after a serious vaginal attempt has proved ineffectual.

Combined Abdominovaginal Operations.—These have been described by Frankenheim, Michon, Delinotte, Aldridge, and Studdiford. The most widely practiced operation is that of Aldridge, which combines an anterior vaginal repair with the introduction of an aponeurotic sling to elevate the proximal urethra and the bladder neck.

The operation has been endorsed in England by Chasser Moir. It undoubtedly gives good results, but has some disadvantages. Personally, I have used this method on five occasions, and each time on a patient with a recurrent cystocele associated with a very severe degree of stress incontinence. On three

occasions it has been completely successful, on one occasion partially successful, and in one patient a complete failure. It is a somewhat tedious procedure and has the theoretical disadvantage of leaving a potential channel of infection between the vagina and the abdomen. In addition the straps are pedicled low down in the abdominal wall to an almost fixed structure. Nevertheless, I am quite convinced that it is a procedure based on sound principles and is ideal for the type of case outlined.

Abdominal Operations.—The simplest of these are the cystopexy of Bonney and the cervicocystopexy of Perrin of Lyons and Everard Williams of London.

Recently, Marshall, Marchetti, and Krantz of New York have developed a form of cervicocysto-suspension which would appear to obviate the disadvantages of cystopexy. I have, to date, had no experience of this operation.

Wilfred Shaw of London employs a sling of fascia lata which suspends the bladder neck and proximal urethra from the pubis. He reports over 50 cases with excellent results. I have not performed this operation to date.

To overcome the disadvantages of the previous methods of abdominal approach, recent interest has centered around some form of aponeurotic sling passed under the bladder neck and proximal urethra from above. The original operations of Goebels and Stockel and that of Hans devised in 1926 have been modified by Millin of London and Marshall of Liverpool, working independently, and it is with the Millin type of operation that I have been closely associated, especially in its modification to overcome certain difficulties encountered in its performance and afterresults. Millin devised his sling operation some five years ago, and to date between us we have performed the operation on more than 200 occasions. I have personally performed 126 such operations to June, 1949. I have naturally preferred this type of operation for the failed vaginal group, and it appears to me to have these advantages:

1. It can be reasonably quickly executed.
2. It does not involve a vaginal incision.
3. The transverse aponeurotic sling is a double sling which has at least the theoretical advantage of being elastic. It is placed in such a manner that any elevation of intra-abdominal pressure is accompanied by further elevation of the bladder neck.

The indication for the Millin sling operation is persistent stress incontinence in spite of one or more adequately performed vaginal repairs without recurrence of vaginal or uterine descent. Patients in this category constitute the 10 to 25 per cent of all failed vaginal repair operations for the cure of urinary leakage during stress. Most patients in this group have experienced more than one attempt at cure, and they may be regarded as the really intractable group. It is submitted that for these unfortunate people an excellent chance of cure can be offered by the Millin retropubic sling operation. With very slight modifications the author submits the details of the operation as published by Millin and himself. It is a purely abdominal operation and affects the suspension of the bladder neck and upper urethra by means of an aponeurotic sling or hammock, which has the particular merit of being elastic, having a muscular pedicle at each extremity. Moreover, by virtue of its disposition, the sling actually tightens when the intra-abdominal pressure rises and bulges out the lower abdominal wall, so elevating the vesical neck under those very conditions which, preoperatively, caused the descent of this structure and so allowed urinary leakage.

Recently, McIntosh Marshall of Liverpool, working independently, has employed a somewhat similar type of sling operation, but his sling is sometimes formed of a free aponuerotic strap of fascia lata. In a personal communication he endorses the claims made for such a procedure.

Millin's Sling Operation

After a full vulval shave, the abdomen is prepared as for any routine abdominal operation. After anesthetization, with full aseptic precautions on the operating table, a No. 20 Fr. Malecot or Foley catheter is passed into the bladder on a stylet. The bladder is allowed to empty and the catheter then gently withdrawn until the expanded head of the Malecot, or the distended 5 c.c. balloon of the Foley catheter is felt to impinge on the vesical neck. If desired, a light pack may be placed in the vagina. The patient is then placed in the full Trendelenburg position and suitably draped. A generous transverse incision is made at the level of the anterior superior iliac spines slightly convex downwards in the line of the skin creases. The incision is carefully deepened throughout its length to expose the aponeurosis of the anterior abdominal wall. The flaps are undermined upward, downward, and laterally, and accurate hemostasis effected by ligature or diathermic coagulation. The anterior sheath of each rectus muscle is now incised in the line of the skin cut, and, by passing the closed blades of a pair of long-angled scissors laterally through this incision, and then gently opening them, the aponeuroses of the two oblique muscles are freed from the underlying transversalis on each side. The incision previously made in the anterior rectus sheath is now continued laterally through the two oblique aponeuroses to within 2 cm. of the anterior superior spine on each side. Both aponeurotic flaps are then freely undermined, and from the inferior one a full-length strap, 1 cm. wide, is cut, pedicled on the right (Fig. 11). A second similar strap is next cut based on the left (Fig. 12). If the straps have been correctly fashioned, it will be noted that about 3 cm. of the base of each is muscular, and so they will have an elasticity not otherwise obtainable. Each strap, 15 to 18 cm. in length, is now wrapped in a warm saline swab. The recti muscles are then separated in the midline, care being taken to avoid opening the peritoneum, and the retropubic space gently opened up by drawing the preperitoneal fat upward. After passing a pair of curved Kocher's forceps from within outward through the middle of each rectus, the end of the corresponding strap is seized and drawn through (Fig. 13), and again wrapped in a warm saline swab. A suitable self-retaining retractor (Millin or Gosset type) is inserted into the wound, and the recti spread. The retropubic space is thus visualized. The bladder neck and upper urethra are gently pushed away from the posterior aspect of the pubis, the attachments being loose and avascular. The expanded end of the catheter will usually be seen, and always felt, so identifying the level of the bladder neck. With finger and thumb, the urethra, with its contained catheter, is traced downward and gently freed from the underlying vagina on each side (Fig. 14). No attempt should be made to isolate the urethra in its entire circumference, or it will probably be torn. Dense adhesions are usually present in the midline on its undersurface, especially after previous vaginal operations. With the proximal urethra elevated with the thumb and forefinger of the left hand, the specially-devised curved forceps, after grasping the apex of the right strap, are now forced through the tough urethrovaginal septum described above, about 2 cm. below the bladder neck, passing from right to left. The apex of the right strap is grasped in forceps by the assistant and withdrawn (Fig. 15). By the slow opening of the blades of these forceps, an adequate tunnel is made to permit the passage of the second strap. The end of the left strap is guided down to the opened jaws of the forceps (Fig. 16), seized, and drawn through. The ends of the straps are held with Kocher's forceps and elevated. Fine Nylon sutures are inserted through the crossed straps on either side of the bladder neck (Fig. 17). A pair of Kocher's forceps is then passed through the junction of the middle and medial thirds of the rectus on each side and the end of the corresponding strap drawn through. The ends of the straps are then sutured to each other with No. 5 Nylon, care being taken that the bladder neck is not unduly elevated, so angulating the urethra (Fig. 18). Two Nylon sutures are used for security. This maneuver approximates the recti and minimizes the risk of divarication. The sling has now, moreover, two points of muscular suspension in the midline in addition to its lateral muscular pedicle.

It is thus seen that by this procedure a double sling is produced. The operation may be modified by the formation of a single sling or hammock simply by relying on the first series of Nylon approximation lateral to the bladder neck (Fig. 18, inset). This is employed if the fascial strips be short, and experience shows that the results of this simple sling are excellent.

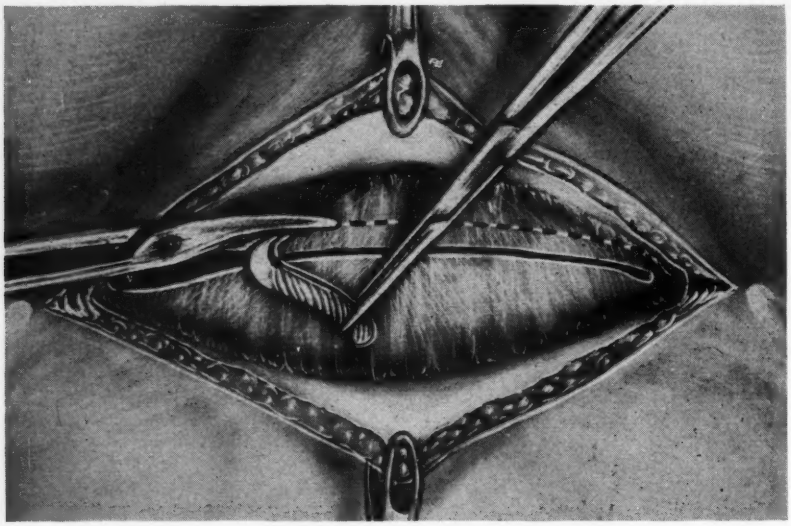

Fig. 11.—Cutting first aponeurotic strap.

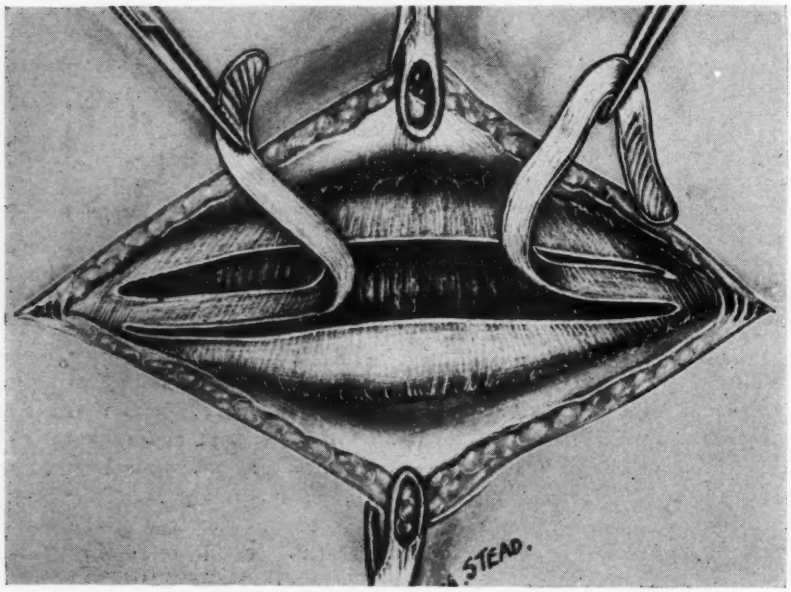

Fig. 12.—Both aponeurotic straps pedicled.

Occasionally venous hemorrhage of a moderate degree of severity is encountered during dissection of the periurethral area close to the bladder neck. This is due to damage to the friable deep vein of the clitoris or its tributaries entering the neighboring plexus, and will usually cease with gauze pressure. Occasionally ligature, or preferably diathermic coagulation, will be necessary.

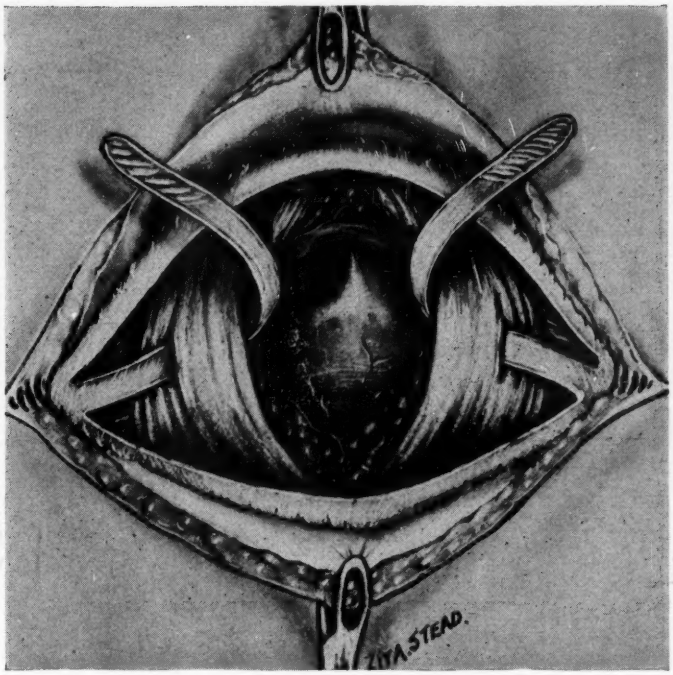

Fig. 13.—Straps drawn through mid rectus muscle into prevesical space.

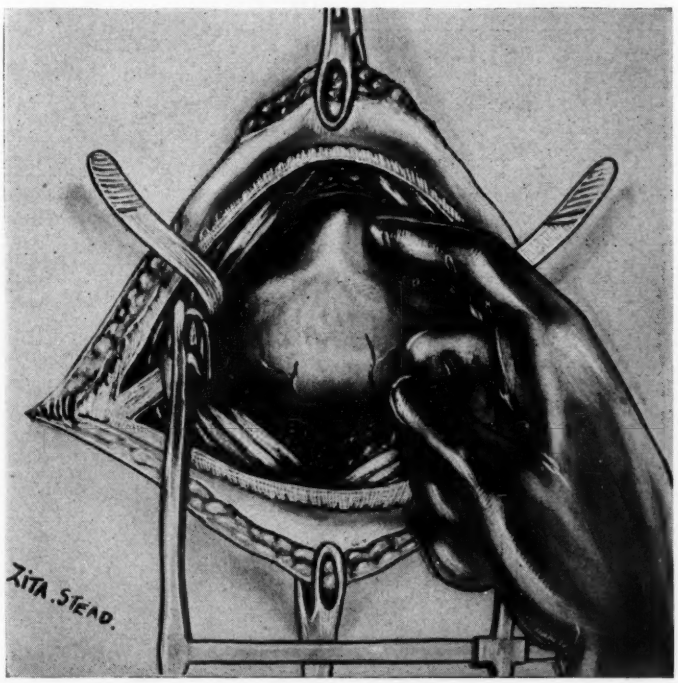

Fig. 14.—Liberation of upper urethra and bladder neck from underlying vagina.

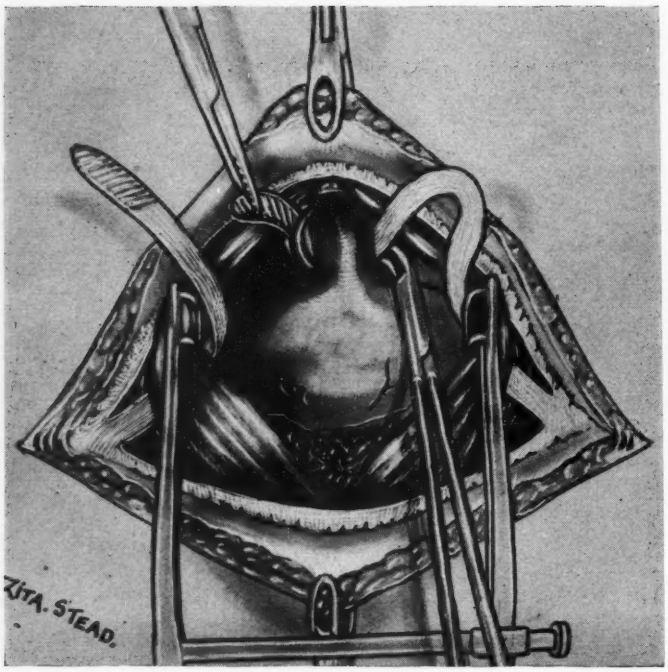

Fig. 15.—The right strap has been grasped by the special forceps and forced through the suburethral space.

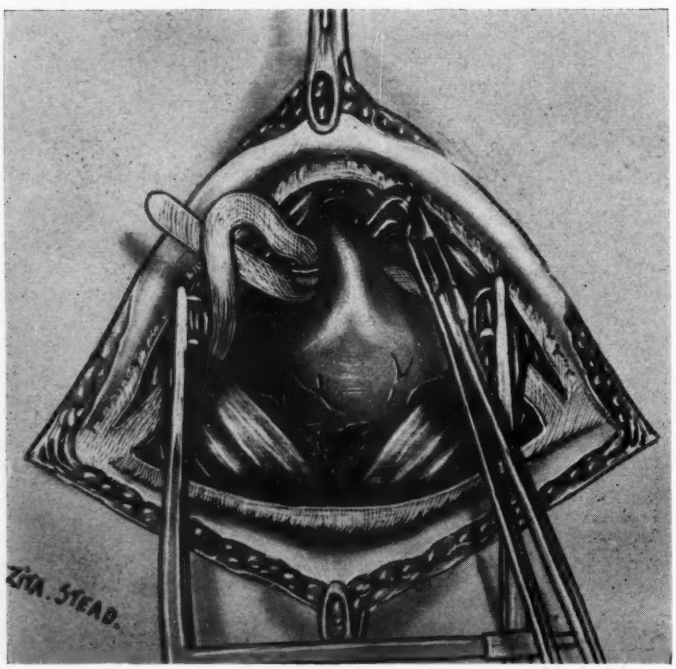

Fig. 16.—Apex of left strap grasped by special forceps and withdrawn through the suburethral tunnel.

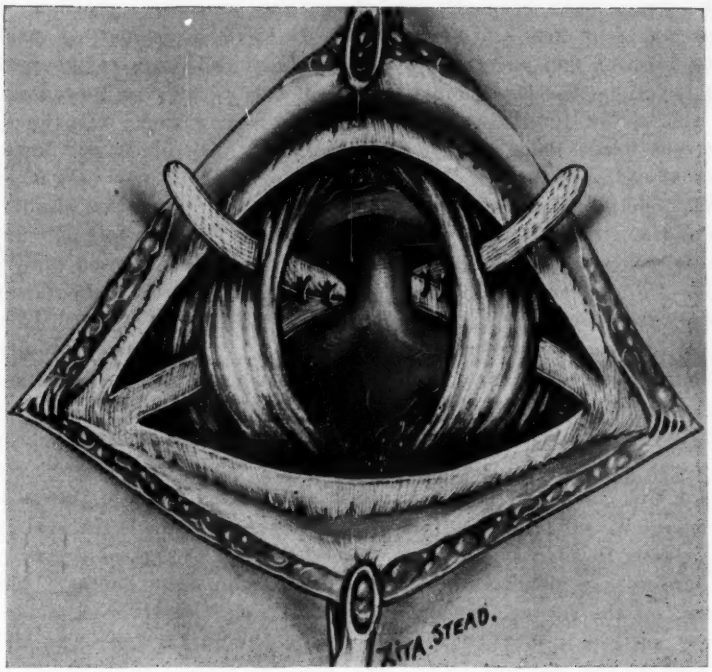

Fig. 17.—Fine Nylon sutures inserted through crossed straps on either side of urethra and free ends of straps drawn through medial aspect of recti muscles.

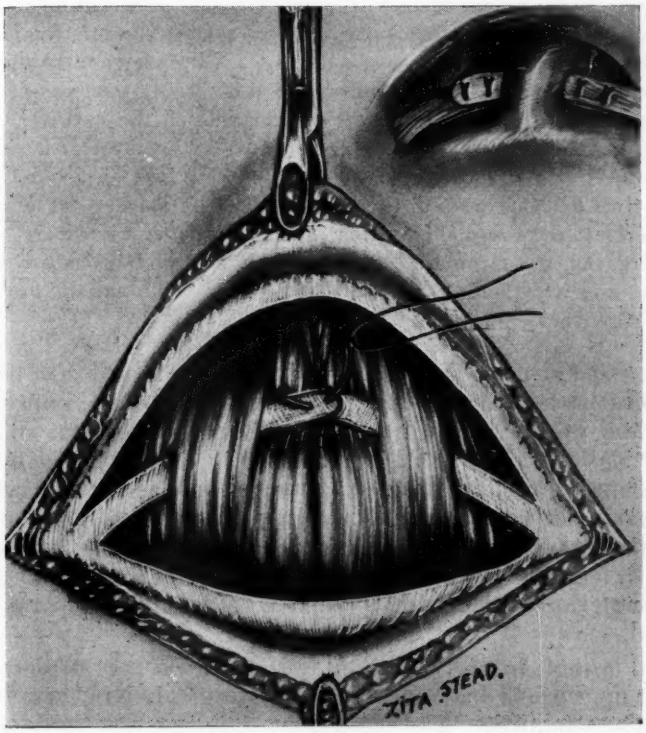

Fig. 18.—Final suturing of strap ends with Nylon.
***Inset.*—Alternative method of single sling or hammock.**

After the straps have been suitably placed and sutured in position, the retropubic space is swabbed free of clots and dusted with sulfanilamide powder. A small stab wound is made in the inferior flap and a corrugated drain placed down to the retropubic space. If the second technique has been employed it will be desirable to approximate the bellies of the recti with a few interrupted catgut sutures loosely tied. (In the first technique the sutured straps approximate the recti sufficiently.) The upper and lower aponeurotic leaves are now united with interrupted sutures of No. 2 chromicized catgut. In some cases the leaves come together in the midline only under tension, and it is desirable to straighten out the table and flex the thighs to reduce the tension. The skin and subcutaneous tissues are approximated with silkworm gut and Michel clips. It is a good plan also to insert a small rubber drain at each extremity of the wound into the subcutaneous tissues to prevent the formation of a hematoma. A pressure dressing is applied. The catheter is irrigated gently to ensure that the bladder drainage is free, and may require an advancement of 2 to 3 cm. into the bladder.

Postoperative Care.—The patient is nursed sitting up in bed; early movements are enjoined. The catheter is connected by sterile tubing to a bedside "Winchester." Irrigations are employed only if the drainage should be faulty. A prophylactic course of sulfadiazine, ½ to 1 Gm. every six hours, is given, and a copious fluid intake insisted upon. A variable amount of sanguineous discharge will escape through the stab wound during the first twenty-four to forty-eight hours, necessitating a change of dressings. The small subcutaneous drains are removed at the end of twenty-four hours. The catheter is usually removed on the seventh postoperative day, but if there is suspicion of injury to bladder neck or urethra it may be advantageously left in for ten days. The retropubic drain is removed on the third or fourth day, and the patient allowed out of bed on the seventh day. She is usually ready to go home on the fourteenth or sixteenth day.

In a small proportion of cases a postoperative suprapubic urinary leak will occur when the catheter is removed. This will necessitate the reinsertion of the catheter for a further few days. With increasing experience we seldom see this complication. It is of little moment, but will prolong the hospital stay. Not infrequently on the removal of the catheter some vesical irritability is noted, but this usually soon passes off. Only rarely is any difficulty of micturition noted after withdrawal of the catheter, but we make it a rule that if urine has not been voided four hours later, the catheter is reinserted. In one early case where this rule was not observed, the retention was discovered only many hours later, by which time extreme vesical distention had led to marked tautening of the straps. Urethral catheterization proved impossible, and suprapubic cystotomy was carried out. In such an emergency, a suprapubic puncture with a lumbar puncture needle would relieve the tension, and a catheter could then be passed. This patient proceeded to a complete cure without further trouble.

Technical Difficulties.—In the average patient these are rare. Previous abdominal operations utilizing the midline subumbilical approach, at times, leave a weakness in the midpoint of the slings but careful dissection of the sheath usually can preserve adequate straps. Previous suprapubic cystotomy may result in dense adhesions between the anterior bladder wall and the parietes, but careful sharp dissection enables the cave of Retzius to be opened readily.

Hemorrhage, from the deep vein of the clitoris or from the associated plexus may occasionally cause a troublesome ooze which will respond to gauze pressure, ligature, or diathermy coagulation. On one occasion only has a massive hematoma developed.

Previous Vaginal Repairs.—In all but four of my patients one or more vaginal repair operations had preceded the sling. In one case there had been twelve previous attempts. The adhesions binding the undersurface of the urethra and bladder neck to the vagina are necessarily denser after vaginal interventions but they yield readily to puncture with the special forceps designed

for the purpose. Most operators undertaking the sling procedure for the first time find the chief difficulty in defining the plane between the urethra and vagina, and are surprised at the force sometimes necessary to perforate the dense bands connecting these structures, especially where several vaginal operations have previously been carried out.

Operations Combined With the Sling Technique.—

On five occasions the author has performed a total hysterectomy, on four occasions a subtotal hysterectomy, and on three occasions a shortening of the round ligaments, in association with the sling technique. This, of course, involves a deliberate opening of the peritoneum, the performance of the intra-abdominal procedure, careful closure of the peritoneum, and a subsequent sling operation.

Complications.—

Postoperative Urinary Obstruction.—In our early cases a desire to make certain of a cure of this distressing complaint tended to encourage overcorrection of the bladder descent, and an unduly tight sling resulted. Following this error in technique a few patients complained of difficulty of micturition, usually shortly after leaving hospital. On endoscopic examination they were found to have, as expected, a transverse ridge at the bladder neck analogous to the median bar obstruction found in the male. In the lesser degrees this will respond to dilatation with a Kollmann's instrument or backward traction to stretch the straps, using a sound in situ. In more severe cases (three in our series) a perurethral resection of the bar was carried out with complete relief of symptoms. Obviously, care must be taken in carrying out this resection to avoid complete severance of the straps, especially in early postoperative days (at a later date the bladder neck has probably become fixed in its high position by adhesions) and, of course, to avoid perforation of the vagina and so cause a vesico- or urethrovaginal fistula.

Sepsis.—This has been encountered in five cases and the result of the operation has been a disappointment in three of these patients. Diffuse retropubic sepsis has resulted in shedding of the Nylon sutures and on three occasions incision and drainage of a retropubic abscess have been necessary.

Postoperative Urinary Leakage.—This will occur in a small proportion of cases but with decreasing frequency as experience grows. Occasionally, when the catheter is removed on the seventh postoperative day, urinary leakage may occur from the stab wound. This indicates that the bladder neck or urethra has been damaged and merely requires reinsertion of the catheter for a few days. In only one case has a fistula persisted for more than twenty days. In this case the sling was too tightly applied and the proximal urethra sloughed with resulting fistula. Repair was effected by the vaginal route some six months after operation, and while the fistula is closed the stress incontinence persists.

Postoperative Urgency.—In some 10 per cent of patients postoperative urgency is experienced to a varying degree. This would appear to be due to irritation of the bladder base by the presence of the fascial sling. In some cases there is a coexistent urinary infection which may be cleared up quickly on a course of alkalis and sulfonamides. Within six to eight weeks this urgency invariably subsides.

Results of Millin Sling Operation

The author has to date personally performed this operation on 126 occasions with a single operative death due to a pulmonary embolus on the tenth postoperative day. The youngest patient was 35 years of age and the oldest 65 years (Table I).

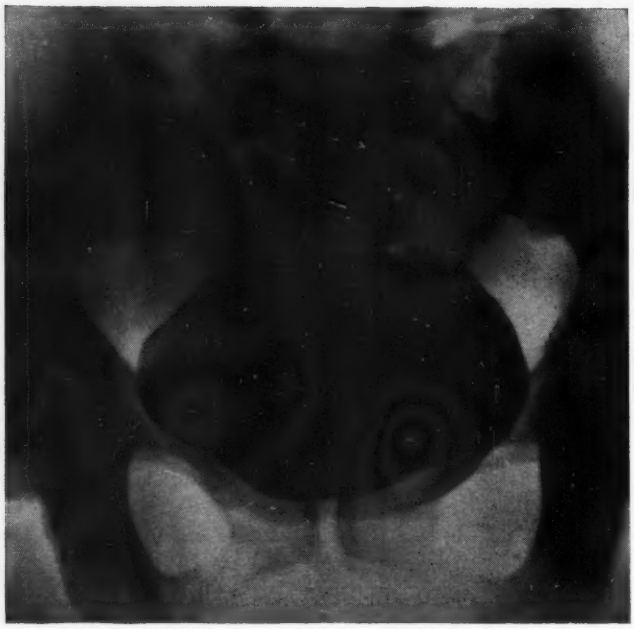

Fig. 19.—Before sling operation.

Fig. 20.—After sling operation. Note bladder base indentations due to sling.

TABLE I. PERSONAL SERIES, 126 PATIENTS

AGE IN YEARS	NO.
30-40	11
41-50	46
51-60	59
61-70	10
Youngest patient	35 years
Oldest patient	65 years

An analysis of the 126 operative results (Table II) shows that ninety-one patients describe themselves as completely cured. Of the thirty-five remaining, twenty-one describe the result as a 90 per cent cure, and these are perfectly satisfied with their result and refuse any further attempt at improvement. Of the remaining fourteen, one is dead and thirteen state that there is no improvement (Table III). One of these was the patient whose urethra was divorced from the bladder neck and subsequently she had her fistula repaired, but she still complains of stress incontinence. Three of the twelve developed postoperative retropubic sepsis and one developed a massive retropubic hematoma which appeared to vitiate the result, and in the remaining eight it would appear that there was insufficient elevation of the bladder neck at operation, a technical fault (Figs. 19 and 20).

TABLE II. RESULTS IN 126 OPERATIONS

Absolute cure	91
Partial cure	21
Failure	13
Operative death (Pulmonary embolus on 10th postoperative day)	1

One of the cured patients had experienced nine previous attempts at cure. In another, failure must be acknowledged with a sling, after twelve previous unsuccessful attempts by other means.

TABLE III. CAUSES OF FAILURE

1. Insufficient elevation of bladder neck	8
2. Severance, by sling, of urethra from bladder neck	1
3. Diffuse retropubic sepsis	3
4. Massive retropubic hematoma	1

Conclusion

I should like to show a color cinema film of the Millin sling operation demonstrating on two separate patients the single hammock sling and the double sling—the latter being simply an extension of the former. Before doing this, however, I should like to correct any impression that I may have conveyed to the effect that I consider this to be the only procedure to be adopted for the failed vaginal repair so far as stress incontinence is concerned. I am certain that cure can be effected by many different sling procedures but the surgeon must adopt that operation which appeals to him and must make himself competent with it. May I again reiterate that a sling of any type is never justifiable in the presence

of uterovaginal prolapse or as a primary procedure without first an adequate attempt at cure via the vaginal route. May I also repeat that a sling operation has no place whatever in the treatment of true urge incontinence; its performance in such cases is disastrous. I hazard the opinion that still more patients with stress incontinence will be cured by the vaginal approach and that the indication for any sling operation will diminish, but at the moment I do feel that this operation offers reasonable hope to those unfortunates suffering from this unpleasant and disabling condition.

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THECA-CELL TUMORS*

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IN ANALYZING the findings in cases of pre- and postmenopausal bleeding admitted to the Montreal General Hospital, we have become increasingly conscious that hyperplasia of the endometrium was demonstrated microscopically in a considerable number of these patients. It has long been accepted that such a pathological pattern of the endometrium indicates excessive estrogen production. Too often, however, the actual source of the estrogen is not considered important. And yet, on the other hand, no matter how thoroughly the individual case may be investigated, conflicting findings render a definite explanation of such a phenomenon highly conjectural.

Where the ovaries appear to be obviously atrophied, it would seem that estrogen, under such circumstances, is probably derived from such an extraovarian source as the adrenal gland. There are, however, a certain number of patients in whom the source of the hyperestrinism, as judged by the endometrial pattern, can be attributed to an existing granulosa- or theca-cell tumor. Even though the ovary may, at times, be under a certain degree of suspicion, it is not considered wise to perform a laparotomy in every case of postmenopausal bleeding exhibiting an endometrial hyperplasia, as, unfortunately, such a procedure would not, in every instance, reveal the actual underlying cause of the hyperplasia. On the other hand, there is no doubt that, were the abdomen opened in all such cases, there would probably be a greater number of estrogen-producing tumors recorded.

Material

Over the period of the past ten years, in a study as yet incomplete, there were over 400 cases of postmenopausal bleeding admitted to the Montreal General and Royal Victoria Hospitals in Montreal. In seven of these, typical theca-cell tumors were demonstrated. During the same period, four other thecal tumors were removed surgically, which were not associated with postmenopausal bleeding. These eleven tumors form the basis for this report.

Histogenesis.—

Novak[1] considers that both the granulosa- and the theca-cell tumors have a common early origin in the ovarian mesenchyme, and that from this progranulosa, protheca type of tissue tumors may arise with potentialities in either of two, or even three directions:

*Presented, by invitation, at the Sixtieth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 8 to 10, 1949.

(a) A nonhormonal type of tumor developing as a dysgerminoma,

(b) A tumor of epithelioid characteristics known as the granulosa-cell tumor, and

(c) A development along connective-tissue lines producing the theca-cell type of tumor.

For the two hormonal types, (b) and (c) above, Novak has suggested use of the term "feminizing mesenchymomas." In certain instances the tumors, when examined under the microscope, present some characters of all three of these types. It is, therefore, upon the predominance of any type of cell that the pathological diagnosis is based.

Traut and Butterworth[2] and others, by the use of irradiation, have experimentally produced follicle atresia and theca-cell proliferation in animals, with ultimate theca-cell tumors. Sturges[3] similarly observed in monkeys the proliferation of the theca elements which accompanies follicle degeneration. There is a very considerable amount of evidence which suggests that, in the human being, follicle atresia, occurring spontaneously, or when artificially induced, may, in a like manner, give rise to theca proliferation with the possible production of theca-cell tumors.

In our small series of such tumors, three (27.27 per cent) patients had at some time been radiated as treatment for their menopausal bleeding. The large number of patients treated annually by radiation for menopausal, or even postmenopausal bleeding, might furnish a fruitful source for the study of such treatment in the production of so-called feminizing tumors of the ovary.

Clinical Aspects.—

It would appear from a recent review of the literature that the age incidence of theca-cell tumors is approximately 50 years. It is worthy of note, however, that though some 65 per cent of these occur after the menopause, 35 per cent do arise during the menstrual life of the patient. The ages, therefore, vary from 16 to 92 years. A true theca-cell tumor in childhood has not yet, to our knowledge, been recorded. In the group herein reported, the ages ran from 21 to 69 years with an average age of 50 years. In 64 per cent of these, the symptoms appeared after the menopause.

The most common symptom of the theca-cell tumor appears to be that of bleeding after the menopause, while in the premenopausal group there is a deviation from the normal menstrual pattern, varying from amenorrhea to menorrhagia. These symptoms, in turn, seem to be dependent on the predominating estrin properties of the tumors.

The so-called Swiss-cheese pattern of endometrial hyperplasia attributed to hyperestrinism is a characteristic microscopical finding. In certain quarters it is held that the estrin produced is possibly from granulosa cells which are frequently seen in thecal tumors, and that a pure type of tumor composed only of theca cells is a rarity. Unfortunately, in many cases, the tumors are removed without any endometrial studies. Such incomplete information obviously vitiates many of the statistics of available reported cases. However, Knight,[4] among others, has reported from collected literature that endometrial hyperplasia was present in 38 per cent of cases of theca-cell tumor. While in our series, in only six of our eleven cases was the state of the endometrium available, nevertheless, of these, one-half showed hyperplastic endometrium. Such a sin of omission as this brings forcibly to mind the definite merit of endometrial biopsies. It should be the abiding rule in all cases of irregular premenopausal, and all cases of postmenopausal bleeding, regardless of the character of any pelvic tumor, to study the endometrium.

It also follows that endocrinological investigation of such patients might be useful as an adjunct in the diagnosis. This should include not only blood studies for estrin and progesterone, but also assays of the tumor itself after surgical removal.

If, as has many times been suggested, prolonged hyperestrinism predisposes to carcinoma, then one might suspect a fairly high incidence of adenocarcinoma of the uterus associated with the feminizing tumors of the ovary. In this regard, a recent report by Woll and co-workers[21] lends further support to such a thesis. They studied the ovaries of patients with carcinoma of the uterus and a comparative series of controls. It is interesting to note that the incidence of thecoma in their carcinoma series was nine times as great as in the control series. We have encountered one case with the combination of theca-cell tumor and adenocarcinoma of the fundus uteri, and it is included in this study.

Uterine fibroids, adenomyosis uteri, and other pathological lesions in the reproductive organs are encountered frequently in conjunction with theca-cell tumors, but the exact interrelationship of these is, as yet, not known. Culiner,[22] in a recent paper, mentions the occasional association of virilism with thecal tumors, but we have not encountered such a syndrome.

Pathology.—

Theca-cell tumors comprise 3 to 5 per cent of solid ovarian tumors. In a paper presented by Dr. F. Falls[20] before this Society in 1948, he reported an incidence of 1.82 per cent out of a series of 1,622 ovarian tumors of varying types collected over a fourteen and one-half year period. In this study, the number of granulosa and the number of theca-cell tumors were approximately equal. In our own group of cases over a ten-year period, theca-cell tumors accounted for 1.8 per cent of all ovarian tumors.

While theca-cell tumors are as a rule unilateral, Falls cites the unique finding of a bilateral tumor.

Thecomas range in size from that of a microscopical tumor to that of a grapefruit or a melon. Again, they may be cystic or solid, the latter, on occasions, being pitted by a varying number of cystic cavities. It appears to be still a debatable point whether these cysts are degenerative in origin, or whether they are, in reality, a cystadenomatous development. Certainly in a large number of cases the theca-cell tumor appears as a firm, rubbery nodule in the wall of a cyst, often enough a dermoid or teratoma, as is illustrated in one of our cases.

Since these tumors on gross examination at the time of operation possess no distinctly identifying features other than, perhaps, the almost constant finding of a yellow or yellowish-orange color, the final diagnosis must, of necessity, rest with the pathologist in the majority of cases.

The microscopic diagnosis with the usual hematoxylin-eosin stains may at times be difficult, as theca-cell tumors may closely resemble fibromas, and possibly spindle-cell sarcomas. The characteristic picture is, however, one of irregular, interlacing bundles or bands of broad spindle cells which are somewhat epithelioid in appearance. Between these bundles may be seen varying-sized bands of connective tissue and often hyaline plaques, the presence of which is fairly typical. The individual tumor cells are fairly regular in size, with usually clear and well-stained nuclei. In a good many tumors, as pointed out earlier, there may be found small groups of typical granulosa cells.

The differentiation of theca-cell tumors from their granulosa-cell counterpart is made easier by the adoption of two special staining methods, both of which should be made a routine procedure in the investigation of any solid ovarian neoplasm.

Theca cells contain fat droplets which are readily demonstrated by Sudan III or other suitable staining techniques, provided that some tissue is retained without fixation for this purpose. Geist[14] has pointed out that this lipoid material is largely cholesterol and its esters in the theca-cell tumor, whereas in the granulosa-cell tumor it is phospholipid and neutral fat. He feels that this fat is not degenerative in origin, but rather is stored and possibly produced by the cells, and may in some way be related to the estrogenic hormone which is usually demonstrated in such tumors. It is important to note, moreover, that in the theca-cell tumor the fatty droplets are found very largely within the cells of the tumor, while in the granulosa-cell tumor, the fat is extracellular, which fact serves as a differentiating point.

Some years ago, Traut[18] and others stressed the importance of reticulum stains as a further method of differentiating the two feminizing types of tumor. They pointed out that the theca cells, whether in the normal follicle, or in a tumor, were always surrounded by a fine connective tissue reticulum, even individually, whereas granulosa cells were not enclosed at all, or only in groups.

We have employed all three staining methods as a routine and the accompanying figures are illustrative examples.

Although a very few cases of theca-cell tumor have been reported which have been considered to be malignant, it is felt by most authors that, generally speaking, the theca-cell tumor should probably be regarded as benign.

Treatment.—

Inasmuch as ovarian tumors can rarely be classified clinically, or at the operating table, certain principles should be adopted for guidance in the treatment of ovarian tumors generally.

In the first place, it should be borne in mind constantly that tumors of the ovary carry a high incidence of malignancy. In the past fifteen years in the Montreal General Hospital, of 695 ovarian tumors of all types, 7.95 per cent of cystic tumors, and 62.2 per cent of all solid types, or an average of 17.9 per cent of all ovarian tumors were considered malignant. Even this figure is considerably lower than that found by some others. For example, Donald MacIntyre found some years ago that, in a series of 782 consecutive ovarian tumors, he had an incidence of 38.43 per cent malignancy. These and other figures would suggest that one should probably assume that all ovarian tumors are malignant until proved otherwise. Unfortunately, however, the histological pattern of some tumors is often a disappointment in giving a malignancy prognosis.

As the size alone is no indication of the degree of malignancy present, or the potentialities of the tumor, one should consider the principle that an ovarian mass of 5 cm. or more in diameter warrants an exploratory laparotomy.

The incidence of malignancy in bilateral ovarian tumors is an indication that radical surgical measures should be adopted. Here the entire uterus, including a small cuff of the vagina, along with both tubes and ovaries, should be resected. A unilateral ovarian tumor presenting any features of malignancy, or a unilateral ovarian tumor in a patient over 45 years of age, even though neoplastic characteristics are not apparent, should be similarly treated. In the younger age group one should rely on the history of the patient and her family, the histological pattern of the endometrium, and the general appearance of the tumor in situ.

When the endometrium associated with postmenopausal bleeding is hyperplastic, one may conclude that such an endometrium has been subjected to estrin influence. Were it not for the present promiscuous use of hormone therapy, the diagnosis of theca- or granulosa-cell tumors would be less complicated. The

practice of the indiscriminate use of estrogens now so common, especially for such vague complaints as "menopausal symptoms," in many instances clouds the issue and renders the interpretation of a biopsy of the endometrium less valuable. Further, it is no doubt true that the prolonged use of certain hormones favors the production of follicle cysts of varying sizes. Under such circumstances the diagnosis of a feminizing tumor of the ovary is all the more difficult. Again, it is our impression that more experience and statistical studies only will determine whether or not estrogenic hormones and such drugs as stilbestrol are carcinogenic. Under any circumstances, with the histological picture of hyperestrinism, one should bear in mind the possibility of the presence of one of the feminizing tumors, particularly after the menopause. If a tumor can at the same time be palpated, the abdomen should be opened and the same surgical principles adopted as those for ovarian tumors generally.

Case Reports

Eleven cases of theca-cell tumor which have occurred in the Montreal General and the Royal Victoria Hospitals in the past ten years are herewith reported. In order to avoid repetition, it may be stated that the pathological diagnosis was made by the study of the gross specimen, and the use of the hematoxylin-eosin, fat, and reticulum stains on the microscopic sections. In all cases the diagnosis was rather clear-cut, and several representative sections are here illustrated.

Fig. 1.—Theca-cell tumor of the ovary to illustrate the general character of the tumor.

CASE 1.—Mrs. G. R. (MGH-4453-45), aged 64 years and para ii, was admitted to the Montreal General Hospital in July, 1945, some 23 years after the menopause. Her only complaint was the presence of an abdominal mass and some bilateral pain, both of which had been noted for two months. She had had a thyroidectomy in 1927. There was no history of vaginal bleeding. Physical examination was compatible with her age, and pelvic examination revealed only a firm, freely mobile mass on the left side. At operation a mass the size

of a grapefruit was found, which was rubbery firm. This, with the entire uterus, was removed. The tumor measured 14 by 14 by 9 cm., was somewhat oval in shape, solid, partially encapsulated, and whitish gray in color. On section, it was yellowish, with some reddened areas, and here and there were cystic cavities filled with a clear fluid.

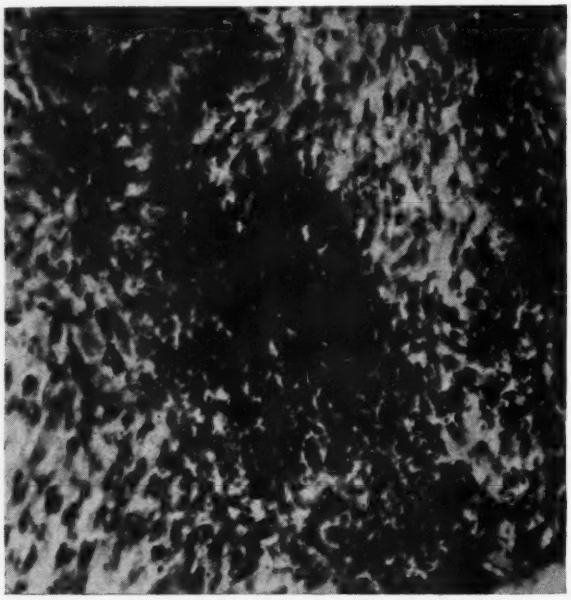

Fig. 2.—Frozen section stained with scharlach R showing the abundant intracellular lipoid in the tumor. (×200.)

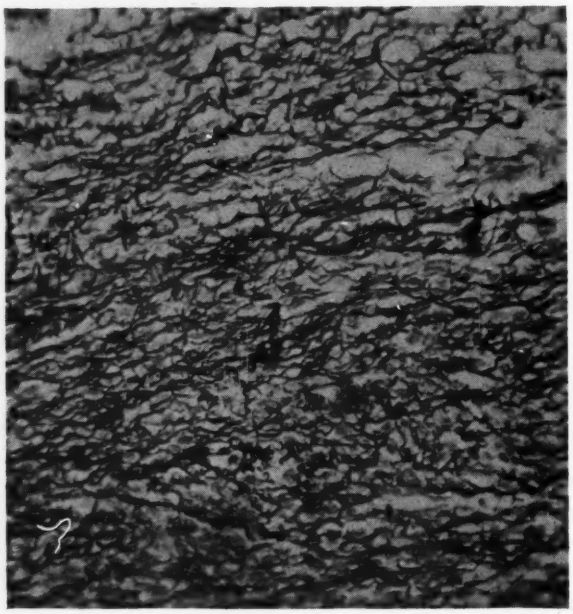

Fig. 3.—Reticulum stain illustrating the abundant intercellular reticulum content of a theca-cell tumor. (×200.)

CASE 2.—Mrs. G. S. (MGH-435-45), aged 69 years and para i, was a woman of good health except for increasing size of the abdomen for the past three months. The menopause had occurred uneventfully twenty-five years previously, and there had been no bleeding since that time. On pelvic examination a small tumor mass was felt on the left side. At operation this tumor was seen to be the size of an orange, and it alone was removed. On section, the tumor was yellowish orange in color, semicystic in consistency, with a solid rubbery part at one end.

CASE 3.—Miss J. L. (OS-MS) was a single woman of 50 years of age, who was five years past the menopause at the time of admission. She had been complaining only of increasing size of the abdomen for five weeks. She had noticed no vaginal bleeding since the change of life. A large tumor mass was palpable on the left side, which was removed entirely at operation. The gross specimen measured 13 by 12 by 4 cm. in size, was in the main cystic, but with a firm, rubbery, hard mass the size of a walnut attached to one side. The color of the firm part was yellowish white.

Fig. 4.—Well-differentiated endometrial carcinoma present in Case 4. (Hematoxylin and eosin. ×200.)

CASE 4.—Mrs. A. P. (MGH-7850-48) was a patient of 62 years of age, para v, who had ceased menstruating seventeen years previously. For six months she had noticed a vaginal spotting and was admitted for diagnostic curettage. A diagnosis of adenocarcinoma of the fundus was made and she was given 2,500 mg. hr. of intrauterine radium treatment. Following discharge from hospital, bleeding continued and she was re-admitted for total hysterectomy and bilateral salpingo-oophorectomy. At operation an ovarian tumor mass was noted, which measured 5 by 4½ by 3 cm. in size. It was grayish white in color, nodular, roughly heart shaped, and somewhat demarcated into lobules. Sections taken from the endometrium at this time showed a still-active adenocarcinoma of the fundus as illustrated in Fig. 4.

CASE 5.—Mrs. H. C. (W-194-48) was a woman of 59 years of age, nulliparous, who, sixteen pears before, had a curettage elsewhere for irregular bleeding, the pathological diagnosis of which is not available. Nine years after the menopause she complained of a sudden

gush of blood and was admitted for diagnostic curettage. The endometrium at this time showed an endometrial polyp and a typical Swiss-cheese pattern of hyperplasia. She was treated by intrauterine radium for a total of 1800 mg. hr. and discharged. Bleeding, however, continued, and two months later, for the first time, a tumor mass the size of a hen's egg could be palpated on the left side. A total hysterectomy was then done, with bilateral salpingo-oophorectomy, and an ovarian tumor measuring 3 by 2½ by 2 cm. was noted. It was quite firm, rubbery, and presented a lobulated, bulging, yellowish-orange surface when cut across.

CASE 6.—Mrs. P. D. (OS-MS), para iv and aged 57 years, was admitted to the Montreal General Hospital, twelve years after the menopause, complaining of stress incontinence. Routine pelvic examination at this time showed a tumor mass the size of a grapefruit on the right side. After repair of the cystocele, both adnexa were removed abdominally. The right ovary was replaced by a cyst which measured about 10 cm. in diameter, with a smooth glistening surface. When it was opened, it was found to contain typical dermoid cheesy material and a "hairball." Attached to one end was a firm mass 2 by 2 cm. in size which was finely lobulated and yellowish in color. The cyst, microscopically, proved to be a teratoma.

CASE 7.—Mrs. G. L. (V-18717-48) was a young woman of 21 years, nulliparous, who complained only of fifteen months' amenorrhea. A diagnostic curettage revealed an atrophic type of endometrium, and under anesthetic a small firm, rounded tumor was palpated on the right side. Laparotomy was later performed and the tumor mass removed. It was the size of an orange, yellowish in color, and firm in consistency. Recovery was uneventful and periods have been quite regular since operation.

CASE 8.—Mrs. T. A. R. (V-16241-48) was a parous woman of 46 years of age, who was admitted to the Royal Victoria Hospital because of irregular periods for the previous four months, during which time there had been some vaginal bleeding every few days. A cystic mass was felt on the right side, and at operation the affected adnexa and the entire uterus were removed. The specimen was only slightly larger than an ovary, but contained a small whitish fibroidlike, firm area about the size of a marble. The endometrium was definitely hyperplastic, and the myometrium contained some small fibroids.

CASE 9.—Mrs. B. B. (V-438-42), para ii and aged 45 years, was a patient who complained of increasing menstrual flow for the previous six months. A year previously a diagnostic curettage revealed a hyperplastic type of endometrium and she was treated by the use of intrauterine radium for 1,800 mg. hr. Bleeding, however, continued, and she was readmitted for laparotomy. At operation the left ovary appeared slightly larger and firmer than normal, so the left adnexa and the supracervical portion of the uterus were removed The ovary was whitish in color, and on section showed a small, firm, yellowish area at one end, which, microscopically, proved to be a theca-cell tumor.

CASE 10.—Mrs. S. W. (V-267057-40) was a woman of 53 years of age, who nineteen years previously had the uterus and right adnexa removed because of fibroids. In 1940 she was admitted to hospital because of vague abdominal pains and the presence on vaginal examination of a firm mass the size of an orange on the left side. At operation this tumor mass measured 6½ by 4½ by 2½ cm. in size, was firm, nodular, and grayish yellow in color.

CASE 11.—Mrs. J. M. (V-12248-45) was a nulliparous woman of 34 years of age with a previous history of chronic pelvic inflammatory disease, and now complaining of sterility, and three months' irregular bleeding. Bilateral cystic ovarian masses were felt on pelvic examination. A supracervical hysterectomy was done and both adnexa were removed. Both cysts were of the simple follicle type, and were yellowish in color, but in the wall of one of the cysts there was a firm area about the size of a pea which microscopically was found to be a theca-cell tumor.

Summary

Theca-cell tumors are discussed relative to their histogenesis, clinical manifestations, pathology, and treatment. A small series of eleven cases from the Montreal General and Royal Victoria Hospitals is reported. These cases are representative of the problems involved in the investigation and management of theca-cell tumors generally. The ages of patients ranged from 21 to 69 years, with an average of 50 years. Seven of the patients were postmenopausal, only two of whom presented bleeding as a symptom. One of these showed hyperplasia, and one an adenocarcinoma of the endometrium. Three other patients demonstrated bleeding as a symptom, two at the menopausal age, and one earlier; all three of these had a hyperplasia of the endometrium. The one remaining patient exhibited amenorrhea as the principal symptom, and, after surgical removal of the thecoma, the menses returned to regularity. Three of the patients in the series had been previously radiated. Theca-cell tumors accounted for 1.8 per cent of all ovarian tumors during the ten years under review.

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Discussion

DR. J. P. PRATT, M.D., Detroit, Mich.—To add another eleven theca-cell tumors to the approximately 100 already reported is a worthy achievement. The brief case reports serve to emphasize some of the features accepted as characteristic of thecomas and again to raise subjects for speculation.

A preoperative diagnosis of thecoma is not yet possible because there is no distinguishing feature. Even at operation it is rarely possible to make the diagnosis. So the chief interest remains with the pathologist.

The author has stated that, given the sign-symptom complex of postmenopausal bleeding, hyperplasia of the endometrium and the presence on vaginal examination of an ovarian tumor mass, one can be at least suspicious of one of the feminizing ovarian tumors. It is agreed

that a suspicion is justified yet there are so many possibilities with this symptom complex that only rarely will the final diagnosis be thecoma. There are many causes of postmenopausal bleeding. Carcinoma and hyperplasia of the endometrium are far more common than thecoma. Other ovarian tumors may be associated with postmenopausal bleeding and the size of the tumor bears no relation to endocrine function. Rarely has anyone been sufficiently impressed with the possibilities to undertake preoperative endocrine studies.

Positive estrogenic assays would not be diagnostic. Jailer found that women in the menopause excrete about the same amount of estrogen as women with amenorrhea or normal women between peaks of excretion during a menstrual cycle. Assay of a thecoma by Knight yielded only 0.2 gamma of estrone per 100 grams of tissue. Many of the thecomas give no evidence of functional activity.

The rarity of bilateral thecomas has been noted. Falls' case was mentioned. Patton and Patton (Illinois M. J. 94: 184, 1948) report a bilateral tumor in a woman, aged 35 years. A few months ago (February, 1949), Dr. C. P. Hodgkinson (my associate) operated upon a woman, aged 55 years, who had a bilateral thecoma. Menstruations were prolonged at age 52. After several months a curettement was done (pathological report not obtainable). Following this operation she had amenorrhea for one year, then she began to spot. Three x-ray treatments were given and there was no bleeding for five months. When bleeding recurred she came for operation. The uterus, tubes, and ovaries were removed. The uterus contained a fibroid and there was hyperplasia of the endometrium. The operator noted that the ovaries contained hemorrhagic follicles but saw nothing else noteworthy. The ovaries measured 3 by 2 by 1½ cm. and 2 by 2 by 2 cm. Thecoma was present in both ovaries.

Statistically, one could say here is another clinical instance in which ovaries have been irradiated and later a thecoma has been found. Inference that there was any relation between irradiation and tumorigenesis is not justified. If the thecomas were responsible for bleeding the tumors were present long before the x-ray treatment. In animal experiments the ovaries treated were actively functioning while in this patient the ovaries were involuted. The three patients who were irradiated as reported by Dr. Sparling were 62, 69, and 45 years of age. It is well known that the effect of irradiation on an aging ovary is quite different than on a young ovary. If the suggestions of animal experiments are to be used for comparable conditions in women, only patients who are irradiated during their active reproductive years should be considered. There is yet no satisfactory human evidence to support this interesting theory.

The increasing tendency to assume a causative relation between the feminizing tumors and carcinoma deserves critical analysis. One of eleven thecomas reported here was associated with carcinoma of the fundus. Claims for carcinogenesis in the uterus by animal experimentation have been on the basis of enormous doses of estrogens. The amount used was far in excess of any estimation of estrogens from thecomas. In fact there is no valid data on the amount of estrogens in blood and urine of patients with thecoma. Until the whole problem of carcinogenesis is clarified we are not in a position to assume a causal relation between thecoma and carcinoma of the fundus. Most of the information about the clinical aspects of thecomas has been obtained in retrospect.

DR. J. P. GREENHILL, Chicago, Ill.—The general impression in the literature is that granulosa-cell tumors are much more common than thecomas and most statistical analyses of ovarian tumors support this belief. However, in some hospitals more thecomas are encountered than granulosa-cell tumors. For example at the Michael Reese Hospital in the years 1942 to 1949 there were 2,986 ovarian tumors of all types of which 325 were solid neoplasms. In this series there were 15 thecomas and only 8 granulosa-cell tumors. Of course, this reversal in the frequency of these two tumors may indicate a difference in interpretation of the criteria of granulosa-cell tumors and thecomas.

There has been considerable discussion as to whether theca-cell tumors constitute a separate group of tumors. As Novak points out, both granulosa- and theca-cell tumors are

derived from ovarian mesenchyme. From the further fact that the biologic properties of these tumors seem to be similar, there is apparently no reason to distinguish the thecoma group from the granulosa-cell tumors. Novak suggested that a more appropriate designation for this whole group is "progranulosa cell tumors" or "feminizing mesenchymoma of the ovary."

Greenblatt and Greenhill (AM. J. OBST. & GYNEC. 36: 684, 1938) reported a case in which the neoplastic elements markedly resembled both granulosa and theca cells. The endometrium exhibited cystic and glandular hyperplasia. This case was reviewed by Walter Schiller who believed it to be an unusual instance of combined thecoma and granulosa-cell tumor. It lends further support to the theory that both the theca and granulosa cells have a common origin from the ovarian mesenchyme.

Both theca lutein cells and granulosa lutein cells contain lipoids. Granulosa-cell tumors as a rule do not, to any marked extent, show lipoid accumulation. It has long been recognized that some granulosa-cell tumors undergo certain degrees of so-called luteinization.

The term, luteinization, should be used with caution. The endometrium very accurately mirrors the endocrinopathies of the ovary. The word luteinization when applied to granulosa-cell tumors, should be reserved for those cases in which the endometrium shows premenstrual or progravid changes. Luteinization and excessive cellular lipoid accumulation are not synonymous. By far the greater number of cases referred to in the literature as luteinized granulosa-cell tumors because of their abundant lipoid content exhibited glandulocystic hyperplasia of the endometrium. This is characteristic of excessive estrogenic stimulation and not of luteinization. Perhaps the term pseudoluteinization is a better one for the cases in which the endometrium is hyperplastic, but not in the secretory phase.

Polariscopic examination of the lipoids in thecomas reveals that they are for the greater part doubly refractile, i.e., cholesterol and cholesterol esters. In our own case an abundance of doubly refractile lipoids was also observed.

Greenblatt, Greenhill, and Brown (AM. J. OBST. & GYNEC. 37: 929, 1939) studied the lipoid content in certain ovarian tumors, including granulosa-cell tumors, thecomas, arrhenoblastomas, dysgerminomas, Brenner tumors, Krukenberg tumors, fibromas, fibromyomas, adenocarcinomas, and others. It seems that fat may be encountered in ovarian neoplasms (exclusive of dermoids and teratomas) in at least three distinct conditions: (1) as a degenerative process, (2) as an inherent capacity of certain embryonal mesodermal tissue, and (3) as a product of tissue metabolism (hormone storage). The granulosa-cell tumors not only vary greatly in their morphology, but vary just as widely in their fat content and yet have a predominantly similar clinical syndrome, that of estrogen stimulation.

What influences the deposition of an abundance of lipoids in certain of the incretory tumors and not in others? When granulosa-cell tumors contain an abundance of lipoids they are spoken of as luteinized granulosa-cell tumors. Theca-cell tumors contain an abundance of lipoids and by the same token are luteinized theca-cell tumors. The evident corollary presents itself that theca-cell tumors may well exist that are not luteinized, just as theca and potential theca cells exist in the normal ovary.

In general we found that the incretory tumors differ from the nonincretory tumors in that the former have a consistently greater phospholipid and cholesterol content than the latter.

All of Sparling's patients are alive and apparently well but this does not mean, of course, that thecomas are benign tumors. These patients must be followed up for many years before a decision can be made concerning the malignancy in each case. A distinct proportion of thecomas, just as granulosa-cell tumors, are definitely malignant. The figure is around 25 per cent. In many instances, the recurrences do not show up for fifteen or more years after the original tumor was removed. On the other hand, death has occurred from metastases within a few months after the removal of these tumors.

What is the proper therapy of thecomas and granulosa-cell tumors? In the majority of cases of theca-cell tumors the women are past the menopause. In Sparling's group of cases, this was true in 64 per cent. I agree wholeheartedly with him that at and beyond the menopause when a thecoma or a granulosa-cell tumor is found, the entire uterus and both tubes and ovaries should be removed. However, in a young woman, if the tumor is entirely within the ovary, and nowhere else, I believe only the involved ovary should be removed.

The relationship between estrogen production in the presence of granulosa-cell tumors, theca-cell tumors, and hyperplasia of the endometrium, and even carcinoma of the endometrium is interesting. I agree with Sparling that there is a definite connection between the estrogen output of ovarian neoplasms and the development of hyperplasia and carcinoma of the endometrium. J. C. Ahumada, R. Sammartino, and J. L. Sardi (Obst. y ginec. latino-am. 6: 34, 1948), in a review up to 1947, found that there were reports of 98 thecomas of which 11, or 10 per cent, were associated with endometrial carcinoma. This high association leads the authors to believe that there is a causal relationship between thecomas and endometrial carcinomas. The carcinoma is due to excessive estrogen stimulation. A preliminary step to the development of the carcinoma is endometrial hyperplasia.

I have a patient from whom, in 1927, I removed an ovarian neoplasm which was believed to be a sarcoma. After Robert Meyer's classic paper appeared in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in 1931, a restudy of the slides from this case revealed an incretory type of tumor, but it was difficult to decide whether it was a granulosa-cell tumor or a theca-cell tumor. This patient had x-ray therapy following operation because of the diagnosis of sarcoma. In 1944, seventeen years later, I removed this patient's uterus and remaining ovary because she had an adenocarcinoma of the endometrium. This case is the reverse of the three encountered by Sparling in which the thecomas were found after radiation therapy. Of course, in my case, the occurrence of endometrial carcinoma may have been entirely accidental and may have had no relationship to the x-ray therapy or the original ovarian neoplasm.

In closing, may I make a plea that we group granulosa-cell tumors and thecomas together, that we practice conservative surgery for the neoplasms in young women and radical surgery in women past 40 years of age, and that we, or someone else, follow up all of these patients for the rest of their lives so that we may learn exactly how malignant these tumors are.

DR. EMIL NOVAK, Baltimore, Md.—Of the many points for possible discussion in Dr. Sparling's excellent presentation, I shall limit myself to three. First, as to the histogenesis of these tumors, this is not included in Meyer's original theory that granulosa-cell tumors are derived from rests of redundant granulosa left over from the formation of the primitive follicles during early embryonic life. As a matter of fact, most of us have abandoned this theory even for granulosal tumors, which quite surely have their origin in the progranulosal and prothecal ovarian mesenchyme. Tumors derived from such a tissue may develop along epithelial (i.e., granulosal) or connective tissue (i.e., thecal) lines, or, as is so commonly the case, they may show a mixture of both granulosal and thecal elements. Granulosal and thecal cells are children of the same mother tissue, the ovarian mesenchyme. As a matter of fact it is unusual not to find an admixture of granulosal cells in thecomas, and this fact helps in their microscopic diagnosis, especially in the absence of differential staining. A thecoma which might otherwise be mistaken for a fibroma will often be properly evaluated if one observes this admixture of granulosal or granulosoid cells.

The second point concerns the provocative recent studies of the Biskinds and others on the production of granulosa-cell tumors and thecomas in intrasplenic or pancreatic grafts of ovarian tissue in previously castrated animals. The estrogen produced by such grafted ovaries is inactivated by the liver, and the ovarian tissue is thus subjected to the unopposed influence of the pituitary gonadotrophic. Why the latter factor should produce the tumors is not clear, though it has been suggested as the responsible one. In any event, this new

line of approach, together with the production of similar tumors in experimental animals by low-dosage irradiation, bids fair to enhance our knowledge of this particular tumor group, and perhaps others as well.

Finally, the fact that thecomas and granulosa-cell tumors produce estrogen makes it easy to understand why they often produce striking effects upon the endometrium, most often shown by benign hyperplasia, but at times by adenocarcinoma. I do not believe that all reported cases of adenocarcinoma in association with estrogen-producing ovarian tumors are authentic, but that some represent the exaggerated estrogen-induced growth picture of markedly adenomatous and proliferative hyperplasia, which can be so easily mistaken for cancer. Since feminizing tumors so often occur during the postmenopausal period, we deal here, as we do in many women without tumors, with the factor of prolonged exposure of the endometrium to the action of postmenopausal estrogen. The source of the latter, in the woman without a feminizing tumor, is believed to be, not the ovary, but the adrenal cortex. A very recent case of my own appears to bear this out. The patient, aged 52 years, had had both tubes and ovaries removed fourteen years previously, but not the uterus. An artificial menopause occurred, with no signs of bleeding until one year ago. Intermittent and at times free bleeding had persisted. Curettage was done, the microscope revealing Swiss-cheese hyperplasia and not the adenocarcinoma which had been suspected. The uterus was later removed, showing extensive and active hyperplasia and no malignancy. The laparotomy confirmed the previous complete removal of the ovaries, and careful search revealed no sign of aberrant ovarian tissue. I believe that the estrogen responsible for the endometrial hyperplasia in this case was of extraovarian origin, probably the adrenal cortex.

DR. JOE VINCENT MEIGS, Boston, Mass.—I would like to draw attention to the work by Wilfred Shaw, published in the *British Medical Journal*, July, 1949, issue, relating to the etiology of cancer of the endometrium. Dr. Shaw showed me cells he considered carcinogenic cells in the ovary. He first found these cells in a woman over 80 years of age with cancer of the endometrium. He later reviewed the slides and found that, in St. Bartholomew's Hospital, these cells were present in 50 per cent of the ovaries in cases of adenocarcinoma of the endometrium. It is possible that if we examine ovaries more carefully we may find these cells described by Shaw.

DR. EMIL NOVAK.—While I am familiar with Shaw's work, and have read his paper on the subject, it seems to me that the evidence which he presented as to the association of certain ovarian hilus cells with endometrial cancer was far from convincing, and the author himself appeared to appreciate this. Moreover, the photomicrographs accompanying the paper were so poorly reproduced that it was difficult to form any clear concept of the cells he had in mind.

DR. OTTO H. SCHWARZ, St. Louis, Mo.—Just recently two Italians discussed this subject in a paper published in April, 1948, in which they described the circulation of the ovary in pregnancy and it seems that actually the cells of the media develop, particularly the veins, and throw out these cells into the adjacent tissue. That is also true of the developing ova. I believe that these cells have nothing to do with cancer or any other type of rare cell.

THE NUTRITIONAL VALUE OF THE ENDOMETRIUM FOR IMPLANTATION AND IN HABITUAL ABORTION*

EDWARD C. HUGHES, M.D., ALBERT W. VAN NESS, M.D., AND CHARLES W. LLOYD, M.D., SYRACUSE, N. Y.

(From the College of Medicine, Syracuse University)

THE basic responsibility of the normal uterus is to prepare a site for the implanting of the fertilized ovum, to produce enough food material for growth and development of the embryo, and to expel the products when they are capable of an independent existence. These physiological processes, under the control of the nervous and endocrine systems, result from the integrated action of the various anatomical segments of the organ. Although all are necessary, the endometrium is the most important, to serve as a source of nutritive material for the blastocyst, particularly before it assumes its hemotrophe formation. It is during the first three weeks of intrauterine life that this vesicle must obtain food from a rather limited source such as the secretion of the endometrial glands, the extracellular fluids of the stroma, the devitalized cells and blood escaping from the damaged capillaries. Ramsey and others have spoken of this substance as "pabulum," while others consider it as "uterine milk." It is during these days that this fragile structure needs a type of food well adapted for rapid growth. It is also during this time that permanent damage can be done to its formation and to its uterine attachment.

We have believed that carbohydrates, being a rapid source of energy and easily assimilated, must be a basic substance of this fluid. We have attempted to observe the metabolism of carbohydrates in the endometrium of 68 normal women, and in 324 patients who have given the history of sterility, abortion, or both. The findings were so uniform in these three groups that it seemed pertinent to include all in the study.

Glycogenesis in the Endometrium

The metabolism of carbohydrates, which takes place in the endometrium, apparently passes through the many chemical changes found in other organs in the body where storage of glycogen is necessary. The following chemical reactions took place in the endometrium as observed histologically.

Glucose was brought to the endometrium by the vascular system of the uterus, the amount of sugar probably being determined by the type of arteriolar development. Once glucose arrived in the endometrium, it was stored as glycogen, awaiting the arrival of the fertilized ovum. It must pass through the various steps of glycogenesis for this storage to take place. It must be phosphorylyzed to glucose 6 phosphate, and through the various stages of poly-

*Presented, by invitation, at the Sixtieth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 8 to 10, 1949.

merization, to glycogen. When implantation was about to take place, glycogen, not being usable per se, was again changed back to a simple monosaccharide, either glucose or fructose.

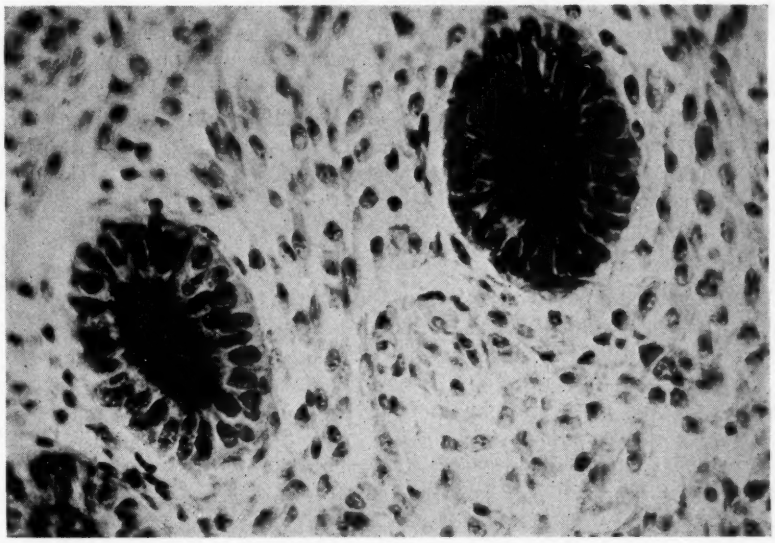

Fig. 1.—Black-staining material is insoluble calcium phosphate, split from hexose phosphate by phosphatases. It appears in the epithelial cells of the gland. (×360.)

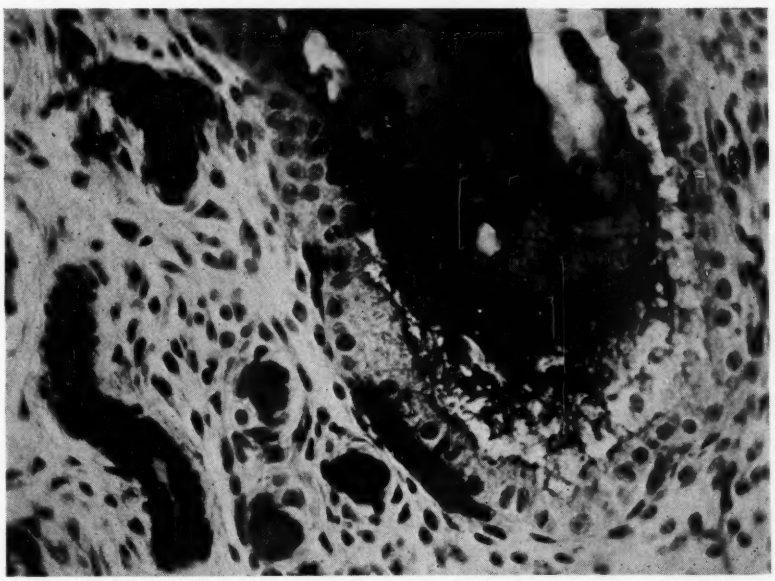

Fig. 2.—Twenty-sixth day endometrium. Phosphatase indicated by black material. Phosphatase is found in the lumen of the gland, and also in the endothelium of the arterioles. A spiral arteriole can be seen in left lower corner, sending three small branches to the gland. The arteriovenous anastomosis can be noted in the gland wall. (×360.)

This histochemical reaction demanded the use of enzymes known as phosphatases, and necessitated the production of these energizers by the various portions of the endometrium. We attempted to follow this process of glycogenesis by noting histologically the distribution of glycogen. Alkaline phosphatase was observed in a smaller group of these patients, while vitamin C and other glycogen enzymes were determined chemically.

Alkaline Phosphatase

Alkaline phosphatase appeared in the arterioles in small amounts prior to ovulation, but it was noted to be present in considerable amounts in the cytoplasm and nuclei of the glandular epithelium at this time (Fig. 1). A secretion of alkaline phosphatase apparently preceded the formation of glycogen. As glycogen was stored, alkaline phosphatase increased in the epithelial cells, and particularly in the endothelium of the arterioles. It was not observed, however, in the epithelial cells regularly at the 26th day of the cycle, but was found in the lumen of the glands in abundance (Fig. 2). The basal arteries, veins, and lymphatics did not contain this material and apparently did not take part in the glycogenesis.

Glycogen

Formation and storage of glycogen began after the secretion of alkaline phosphatase in the epithelial cells of the endometrial glands. It was accumulated at the base of the cells at about ovulation time, causing the nuclei to be pushed up to the mid-portion of the cell.

In the secretory time, glycogen in globule form passed to the periphery of the cell, where it was converted back to fructose (Fig. 3).

It was interesting to observe that alkaline phosphatase was not present in the epithelial cells where further steps in glycogenesis must have taken place. There must have been other enzyme secretions at this time, which were not demonstrated by staining methods. Chemically, we found and quantitated a glycogen-splitting enzyme, which was particularly active at this time. The amount of this enzyme varied in different stages of the cycle. The following table shows the amounts as expressed in milligrams per gram of tissue:

DAY OF CYCLE	MG. PER GRAM OF TISSUE
1 through 6	11.5 mg.
7 through 15	15.6 mg.
16 through 23	30.6 mg.
24 through 26	30.9 mg.
26th	36.9 mg.

Vitamin C

Although the role of this vitamin in this process is not known, it was found in rather consistant amounts in the endometrium. Chemically, it ranged from 164 micrograms per gram of tissue in the early portion of the cycle to 168 micrograms per gram of tissue in the latter part of the cycle. Histologically, it reduced silver salts during the secretory phase, particularly in the epithelial cells of the uterine glands.

The endometrium must develop to the full secretory stage and pass through the normal histological changes that take place during the cycle to have this normal glycogenesis. The spiral arterioles, particularly, play an important part in this mechanism. In the normal, their walls became hypertrophied except at their distal ends and near the glands, where they terminated in a network of capillaries. The endometrial glands increased in length and size, pouring forth large quantities of secretion. The stroma became edematous, containing an almost mucoid type of fluid (Fig. 4).

This entire process of glucose metabolism in the uterus as observed histologically seemed to be in keeping with the theories of glycogenesis noted elsewhere. It has been stated that there must be a phosphorated intermediate such as a Cori ester for this transformation. Our observations are in agreement with those made by Wislocki and Dempsey. We have used these observations to evaluate the quality of the endometrium in the 324 patients of this series.

Nine hundred ninety-six endometrial biopsy studies have been conducted on these patients.

Material and Methods*

The entire series had complete sterility studies. All samples of endometrium were removed on the twenty-sixth day of the cycle, for it was found that tissue removed later was not consistent for the materials under consideration. Con-

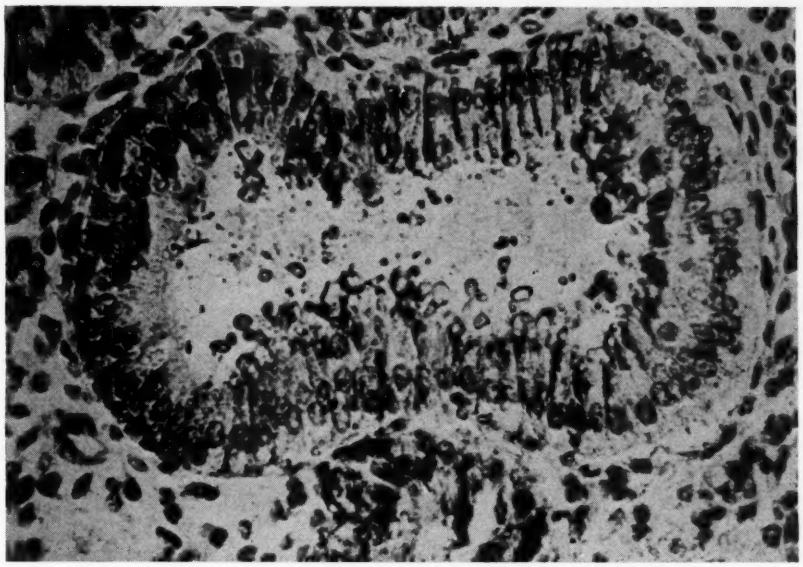

Fig. 3.—Glycogen staining deep red, but indicated in the above section as black granules pouring forth from the epithelial cells into the lumen of the gland. (×360.)

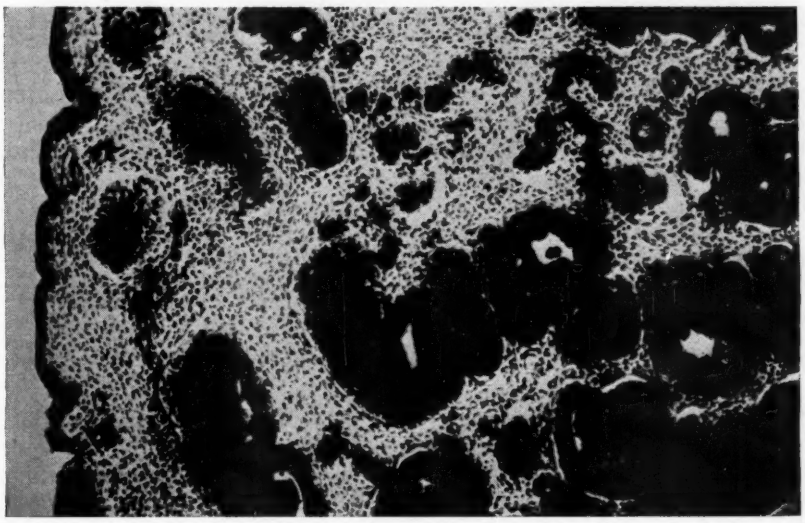

Fig. 4.—Glandular development with phosphatase reaction is marked. Arteriolar staining is noted. Stroma shows normal edema.

*The alkaline phosphatase and vitamin C were studied in the Department of Pathology, Syracuse University, under the direction of Dr. Herman Dick and Dr. David Jones. The chemical determination for vitamin C was done using the method of Roe and Keuther in the Department of Pharmacology by Dr. J. Tepperman. A more detailed report of these substances is in process and will be published later.

trol sections of normal endometrium were stained at the same time as each specimen under observation. Specimens were fixed in 95 per cent alcohol for glycogen and alkaline phosphatase; in 10 per cent formalin for the usual hematoxylin and eosin stains. These sections were used as a control for the proper estimation of the cycle date. Sections were stained for glycogen by a modified carmine stain. Alkaline phosphatase sections were stained using a modification of the Gömöri method. Staining method of the vitamin C was a modification of the Barnett and Bourne procedure.

Evaluation of the Endometrium

We found that glycogenesis and these histological changes in the uterus did not proceed normally in 58 per cent of the 324 patients described earlier. There occurred minor or major deficiencies in the endometrium, which, we felt, gave a basis for the cause of the sterility and abortion. The following chart shows the percentage of endometrial changes:

TOTAL PATIENTS STUDIED		(324)	TOTAL PREVIOUS ABORTIONS		(148)
Sterility patients	176		One previous abortion	42	
Aborters	77		Two previous abortions	54	
Both	71		Three or more abortions	52	
		324			148

PERCENTAGE OF ENDOMETRIAL CHANGES

PROBLEM	CASES STUDIED	NO.	PER CENT
Sterility	176	77	43
One previous abortion	42	23	54
Two previous abortions	54	45	83
Three or more abortions	52	45	86

58 per cent showed endometrial failure
42 per cent due to other abnormalities

The following changes were observed in the endometrium:

1. The endometrium did not proceed to the twenty-sixth day of the cycle in 15 per cent of the patients, although all biopsies were removed on that day. The glands remained in the proliferative state, the stroma was compact and without edema, while the arterioles were underdeveloped and did not assume their spiral configurations. Alkaline phosphatase was secreted in abundance in the epithelial cells, but glycogen was scanty, or did not appear at all (Fig. 5).

2. Unusual distribution and smaller amounts of glycogen and alkaline phosphatase were noted as compared with the controls, although the pattern did proceed to the twenty-sixth day (Fig. 6).

3. The glycogen-splitting enzyme in seventy-seven patients was below normal, averaging 16.6 mg. per gram of tissue.

Disregarding the male factor entirely, the sterility and infertility in the other 42 per cent were due to other abnormalities such as retroversion, cervical pathology, leiomyomas, tubal occlusion, etc. The endometrium appeared normal in all cases of this group. Although it may seem high that 58 per cent had deficient endometrium, it is a fair statement that it was the only significant finding in these patients. On this basis, it would appear that a faulty endometrium is a fundamental cause for sterility as well as abortion. It has brought up the problem of how these changes were related to these conditions. It may be said that a healthy endometrium in a full secretory state is best for the free blastocyst and immediate implantation. It could be theorized that a poor tissue, scant in the essentials of nutrition, might cause death of the ovum before implantation could be accomplished, thereby causing sterility. In this type of patient, the

egg itself might not be normal. The combination of these two conditions would be serious.

Pathological studies of 106 abortuses in patients included in this group have shown changes in the decidua and chorion that strongly suggest an improper nidation and poor nutrition as a basis for the abortion. The abortuses of eight patients were examined after each of two abortions, while the products in three patients were studied after three successive abortions. Each time, the pathological pictures were similar. The following findings were noted:

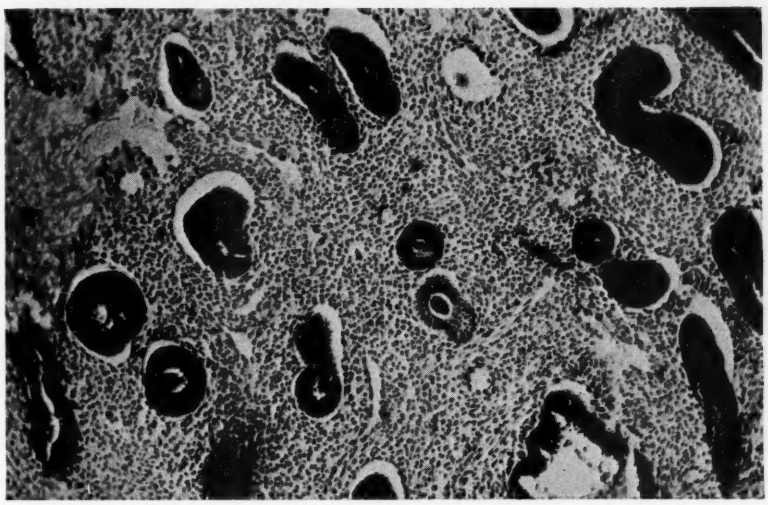

Fig. 5.—Endometrium remained in the proliferative phase. Epithelial cells contained large quantities of alkaline phosphatase, but practically no glycogen. (×85.)

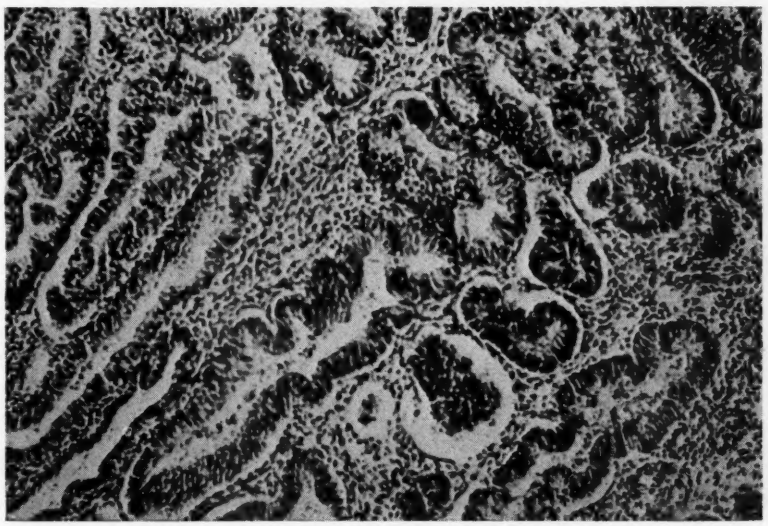

Fig. 6.—Endometrium typical of the twenty-sixth day tissue, but glycogen and alkaline phosphatase are contained in a few glands. Glycogen is noted as black granules in the lumen.

1. Thrombosis, hemorrhage, and necrosis of the decidua were noted, which would influence the blood supply to the trophoblast.

2. Failure of development of the chorionic villi occurred, with these structures remaining in an immature state. Langhans' layer was particularly under-

developed and, in some villi, these cells were entirely missing. The embryo failed to grow in keeping with the length of gestation and in many cases it was not found at all. This type has been designated as the blighted ovum.

3. Premature separation of the placenta with circumvallate development was observed in those that aborted at later dates.

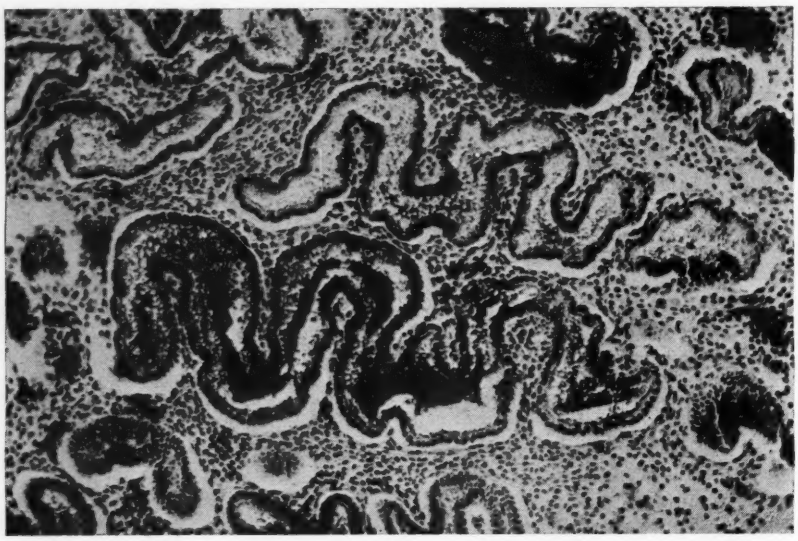

Fig. 7.—Endometrium before treatment. Secretory phase with poor arteriolar development. Glands contain alkaline phosphatase irregularly. Glands are sectioned sagitally. ×85.)

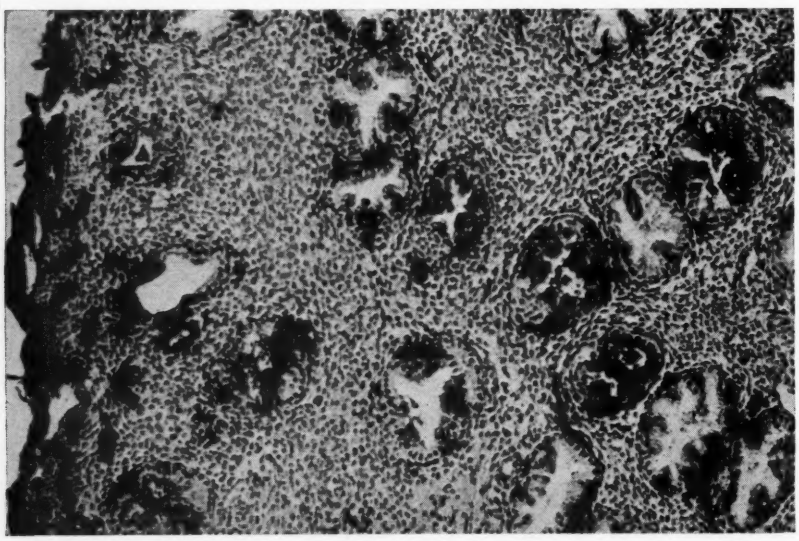

Fig. 8.—Endometrium after treatment. Marked arteriolar proliferation; some changes in the stroma. Capillaries are demonstrated in the wall of the gland and under the surface of the endometrium. Gland sectioned transversely. (×85.)

Inasmuch as these pathological conditions were found in those patients with deficient endometrium, we have placed the cause on a nutritional basis. It has been necessary to establish reasons for such alterations, particularly to institute proper treatment. This has been approached from an endocrine stand-

point, inasmuch as no physical basis for these conditions has been found in these women. Before we established our laboratory for standardized methods of endocrine determination, various glandular methods of therapy were tried. Small doses of estrogen proved most effective. Diethylstilbestrol, 0.1 mg., or 0.325 mg. of Premarin, given for twelve nights after cessation of menstrual flow, was found to be the effective dose. It had the following effect upon the endometrium:

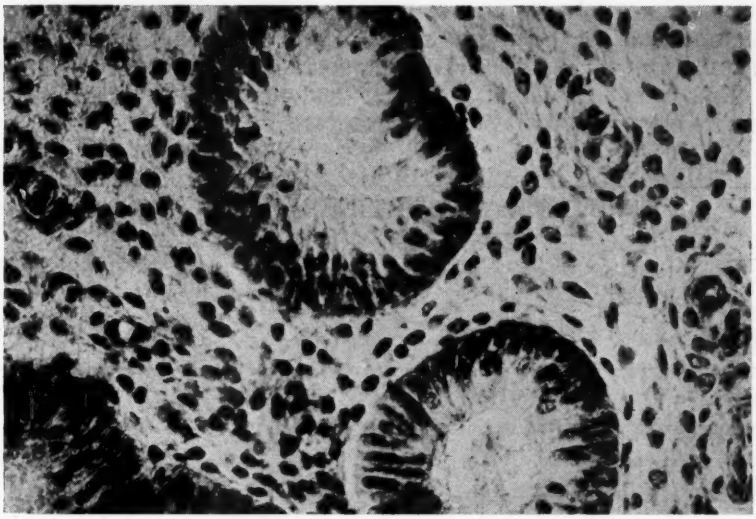

Fig. 9.—Endometrium removed twenty-sixth day from sterility patient before treatment shows proliferative phase with slight glycogen. Alkaline phosphatase was found in large quantities in these epithelial cells. (×360.)

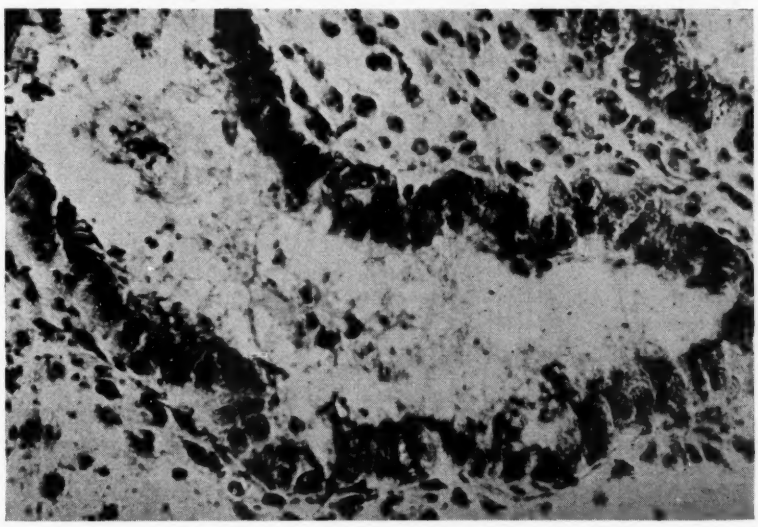

Fig. 10.—Same patient as in Fig. 9. Twenty-sixth day sample of endometrium after treatment. Secretory phase with large amount of glycogen in the cells. Glycogen stains black.

1. The arterioles became longer and more developed. The capillary tufts about the gland became more prominent and filled with alkaline phosphatase.

2. The endometrial gland also assumed a secretory state, pouring forth more glycogen and alkaline phosphatase.

3. The entire endometrium became a true secretory type of tissue.

Fig. 7 shows the endometrium before treatment, removed from a patient with a history of two spontaneous abortions. Fig. 8 illustrates the marked vascular improvement in this patient after medication.

Fig. 9 presents endometrium removed from a sterility patient before treatment, and Fig. 10 shows the endometrium of the same patient after treatment. Both samples were removed on the twenty-sixth day of the cycle.

The question then arose as to the reasons why these small doses of estrogen should have such an effect. It was postulated that it could be due to either ovarian, endometrial, or pituitary stimulation. It was thought that estrogen caused the pituitary to produce more gonadotropins, particularly the luteinizing factor in these women. Dr. Lloyd has demonstrated in our laboratory that estrogen did increase the LH level in the castrate.

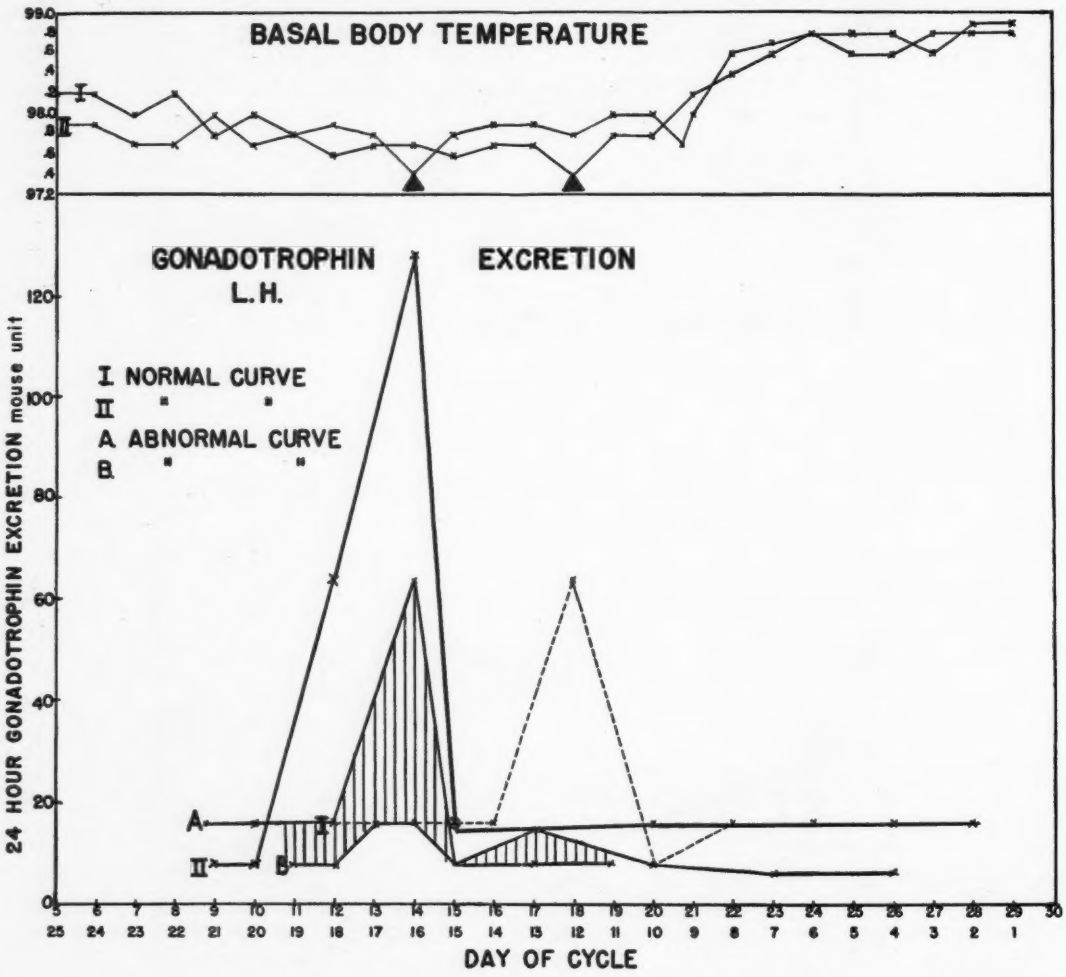

Fig. 11.

Further to substantiate these findings, total gonadotropin determinations were done in normal patients and in twelve women in this series. The follicle-stimulating hormone assays were determined by the ovarian hyperemia procedure developed in our laboratory, and previously published. The important

change was noted in the level of LH. These levels were below normal in all cases, ranging from less than 16 mouse hyperemia units to 64 units, while the amounts generally reached from 64 to 128 mouse hyperemia units in the normal (Fig. 11).

In several patients, after administration of small doses of estrogen, the LH levels increased, followed by an improvement in the basal temperature curve and the endometrial picture. Diminished amounts of LH in these patients apparently accounted for the poor luteotrophic effect as reflected in the endometrial pattern.

When the total gonadotropins were low, as particularly indicated in the endometrial picture, endocrine therapy was of little value. However, those with low LH levels responded to treatment with good results. In these individuals, however, it was important that treatment be given prior to pregnancy or the desired effect would not be attained. We have used this treatment in 126 patients with the following results:

Abortion Cases.—Fifty patients treated, ten failures. All patients treated in this group had had two or more spontaneous abortions.

Sterility Cases.—Seventy-six patients treated, thirty-one failures.

Conclusions

The present study concerns the metabolism of glucose as shown by histochemical stains of the endometrium of normal women and patients giving the history of sterility and abortion. The endometrium has been studied for glycogen, alkaline phosphatase and vitamin C and other enzymes. Certain preliminary conclusions can be drawn.

Failure of the endometrium to produce adequate amounts of carbohydrates appears to be a cause of sterility, and, particularly, of habitual abortion. The determination of the secretory activity of the endometrium serves as an important index in determining the cause of sterility and abortion. Lack of preparation of the endometrium is primarily due to failure of the pituitary to produce adequate amounts of LH for corpus luteum stimulation. Small doses of estrogen will improve the secretory ability of the endometrium by stimulating the output of LH. Fruitful pregnancy requires treatment before fertilization. Frequent studies of the endometrium and abortuses are of definite value.

This work was aided by a grant from Ayerst, McKenna and Harrison, Limited, New York, N. Y. I would also like to acknowledge the assistance of Dr. Norbert Reicher, who examined each endometrial biopsy, and the laboratory work done by Mrs. M. E. Hawkins and Mrs. K. M. Weiskotten, as well as the photographic work done by Miss Stella Zimmer.

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Discussion

DR. JOHN PARKS, Washington, D. C.—Dr. Hughes and his co-workers have combined the facilities of the laboratory and the experiences of the clinician to emphasize the nutritional importance of the endometrium during that all-important period of embryonic develop-

ment in which the fertilized egg takes root and begins to grow off the substance of the uterine bed. The whole process of intracellular carbohydrate metabolism has received considerable attention by investigators of metabolic diseases and vitamin deficiencies. It is significant that the authors have applied methods of evaluating glycogenesis to the uterus, an organ whose tissues change with some degree of periodicity. The role of vitamin C and the exact nature of the various glycogen-splitting enzymes would seem to be beyond the scope of this particular discussion.

It is of clinical significance that alkaline phosphatase has been demonstrated in the endometrium during the preovulatory phase and that it tends to disappear just prior to menstruation. This is in agreement with the work of Atkinson and Engle (Endocrinology 40: 327, 1947) who found that estrogens caused an increase in uterine phosphatase. Secretion of alkaline phosphatase has been found to be followed by the storage of glycogen. By his excellent slides, Dr. Hughes has demonstrated that deficient glycogenic properties are evidence of a poorly prepared endometrium for the implantation of a fertilized egg. This confirms Zondek's impression that reduced glycogen in the secretory endometrium is an important contributing factor to infertility.

From their wide experience in the staining and interpretation of endometrial specimens and from their evaluation of the products of abortion resulting from patients with glycogen-deficient endometrium, the authors have brought out several points of practical clinical interest. Reference to the development of circumvallate placentas in patients with faulty glycogenesis seems to fit into the theory that poor endometrial nutrition is a background for this particular placental abnormality. From the work presented, it is suggested that a poor endometrium can prevent the implantation of a normally fertilized egg, and that if implantation does occur in such an inadequately prepared endometrium, abnormal development of the ovum may result. Importance has been placed on the taking of endometrial specimens on exactly the twenty-sixth day of the cycle. Since some of the patients investigated may have had irregular menses. It would help to know how the cyclic dates were determined and whether or not any early pregnancies have been removed inadvertently. The authors have indicated that small doses of estrogens in the early phase of the cycle increase gonadotropins. It would be interesting to know whether or not these same patients showed an increase in alkaline phosphatase after receiving estrogens.

In his evaluation of patients with abortion and sterility, Dr. Hughes has recorded his failures. Therefore, it is presumed that four out of five of his patients with previous abortions were successfully carried through subsequent pregnancies, and that forty-five out of seventy-six patients with reduced fertility had their problems corrected. Such a percentage of success in treating these two tremendous problems in obstetric practice would indicate that a great deal of time and study has been devoted to each patient, and that this report represents a selected group in which only the factor of deficiency in glycogenesis was an important finding.

That treatment of relatively afertile patients be started prior to conception is an excellent recommendation. The authors have presented a clinical method of diagnosis, and of evaluating and treating those women who show a reduction in endometrial glycogenic properties.

DR. WILLIAM F. MENGERT, Dallas, Tex.—The author is to be congratulated for a well-conceived paper of fundamental importance concerning histochemical reactions of the endometrium. His paper emphasizes that failure of the endometrium to produce adequate amounts of carbohydrates appears to be a cause of sterility and, particularly, habitual abortion. Few would presume to deny the correctness of this contention, and we must therefore include endometrial insufficiency with other basic causes of fetal abnormality, such as congenital anomaly and maternal virus disease.

It would seem that when abortion occurs as the result of a nutritionally deficient endometrium all parts of the product of conception should be affected. In other words, in the case of blighted ova with absence of the embryo, as noted by the author, are we justified

in the assumption that this is on a nutritional basis, rather than due to some anomaly of the zygote before it encounters the environment of the endometrium?

According to Wislocki and Dempsey, there is no tissue glycogen in the endometrium of the sow at any time during the reproductive cycle, or in the placental region. There are moderate amounts in cat endometrium shortly after implantation, but none in the placental region. On the other hand, glycogen appears in the endometrium of rodent, macaque, and man during the secretory phase and is present in quantity during gestation.

Because of this, and other sustaining evidence, these authors feel that glycogen is deposited in poorly vascularized regions of the endometrium and suggest that tissue glycogen as a source of energy is unnecessary in regions of good vascularity. It would be interesting to know about endometrial glycogen and the carbohydrate supply available to the embryo of the poorly controlled diabetic woman carrying consistently high blood-sugar levels, especially in view of her known propensity to sterility and abortion.

It would also be helpful, for the sake of comparison, to know the percentage of glycogen deficiency in the endometrium of a numerically equal control group of normally fertile women.

DR. HUGHES (Closing).—I have taken endometrial biopsies on six patients who were pregnant. I did not do it intentionally. All proceeded to term without difficulty.

In regard to treatment with small doses of estrogen, there was an increase in the glycogen and also the alkaline phosphatase in the endometrium if small doses were given.

I am not prepared to make a statement on the effect of estrogen therapy improving the blood supply to the glands.

In the case of the blighted ovum, I think the ovum may be poor on the same basis that we have a poor endometrium. It may be a poor endometrium from the start. The levels of glycogen seem to be low in the endometrium of diabetic patients.

SARCOMA OF THE UTERUS

An Analysis of 42 Cases

K. T. MacFarlane, M.D., F.A.C.S., Montreal, Quebec

(From McGill University, and the Montreal General and Royal Victoria Montreal Maternity Hospitals)

SARCOMA of the uterus is encountered in gynecological practice so infrequently that any individual's personal experience with the disease must be limited. Consequently, the literature reveals some variance on many aspects of these tumors, even their degree of malignancy. Unquestionably there are degrees of malignancy in tumors designated as sarcoma in other regions of the body. This would appear to be equally true of uterine sarcoma. The inclusion of dubitable cases in some series has resulted in a higher incidence, a better survival rate, and a false impression of the possible seriousness of the disease. In our experience, the frank case of sarcoma is an extremely lethal disease which presents a serious problem. A clear conception of the clinical picture and the pathogenesis of the disease is imperative if we are to carry out intelligent treatment.

Since its first description[1] about ninety years ago, many reports have appeared in the literature. The one salient feature apparent is the difficulty in diagnosis. A clinical diagnosis is rarely made and even at operation the exact nature of the lesion is often in doubt. Frequently the pathological findings and interpretation of the histological characteristics are equally difficult. The varied opinions expressed by pathologists, which we have encountered, strengthen our opinion that often the experience of the pathologist is the major factor in the diagnosis of these cases. In an effort to correlate the clinical findings, the pathological diagnosis, and the ultimate outcome in a series of such cases this study has been instituted.

Material

The data reviewed were obtained from the case records and the pathological material of forty-two cases of histologically diagnosed sarcoma of the uterus occurring at the Montreal General and the Royal Victoria Montreal Maternity Hospitals during the twenty-year period of 1929 to 1949.

The pathological material was carefully reviewed with the cooperation of the pathologists of the two hospitals and all doubtful cases were excluded. The majority of these consisted of cellular myomas showing none of the usual histological criteria of malignancy.[2] In addition, a few cases were judged to be unsubstantiated because of inadequate specimens which in most cases were obtained by curettage or biopsy. Several cases originally diagnosed as sarcoma were rejected when review failed to confirm the original opinion.

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*Presented, by invitation, at the Sixtieth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 8 to 10, 1949.

There were during that period 52,322 gynecological admissions, making an occurrence of 1 in 1,245 admissions. Approximately 42,439 pathological specimens were examined from these admissions, the lesion therefore appearing once in 1,010 specimens, or about 0.10 per cent.

TABLE I. INCIDENCE OF UTERINE TUMORS IN 42,439 GYNECOLOGICAL SPECIMENS

TYPE	NUMBER	PER CENT
Benign myoma, fibromyoma, etc.	5,165	12.17
Squamous carcinoma of cervix	1,149	2.71
Adenocarcinoma of cervix	108	0.25
Carcinoma of fundus	397	0.94
Sarcoma, all types	42	0.09

The incidence of other uterine tumors, both benign and malignant in the same period, was in keeping with general statistics.[3-8] Benign tumors composed 12.17 per cent, cervical cancer 2.96 per cent, and fundal cancer 0.94 per cent of the specimens. The relative incidence of sarcoma to benign and malignant uterine tumors was also calculated. It comprised 2.53 per cent of the malignant tumors of the uterus (excluding chorionepithelioma). In relation to leiomyoma it occurred with a frequency of 1 in 123, or 0.81 per cent.

TABLE II. RELATIVE INCIDENCE OF SARCOMA TO OTHER UTERINE TUMORS

	FREQUENCE	PER CENT
Sarcoma to benign myoma	1 in 123	0.81
Sarcoma to malignant tumors	1 in 39	2.53

The average age recorded in the series was 50.9 years, the youngest patient being 22 and the eldest 74 years of age. The largest group, 12 cases (28.6 per cent), occurred in the fifth decade, while 76.2 per cent of the entire number were between 40 and 70 years of age.

TABLE III. AGE INCIDENCE OF 42 PATIENTS WITH SARCOMA OF UTERUS

AGE	NUMBER	PER CENT
21 to 30 years	3	7.1
31 to 40 years	5	11.9
41 to 50 years	12	28.6
51 to 60 years	10	23.8
61 to 70 years	10	23.8
71 to 80 years	2	4.8

The youngest patient in the series, Case 7, who was 22 years old when the disease developed, had had a case of primary amenorrhea. A simple cyst of the right ovary had been removed at the age of 20 years. The present condition had begun with vaginal bleeding and a cervical polyp about six months before final diagnosis was made. In the intervening time the uterus had been curetted on three occasions for a recurrent polypoid condition of the cervix which microscopically revealed evidence of chronic cervicitis and exudative endometritis. The specimen from the third curettage showed a peculiar myxomatous appearance with cellular structure suggesting sarcomatous tissue. Hysterectomy was done at once and an anaplastic endometrial sarcoma was found. The disease proved fatal within six months.

Relation of the disease to parity was not instructive. Twenty of the patients were nulliparous and twenty-two had borne children. The menstrual histories were not remarkable, the menarche in 62 per cent of the patients being from age 12 to 14 years. Twenty of the patients, whose average age

was 42 years, were still actively menstruating. The remaining twenty-two patients were post-menopausal, with an average age of 60.3 years. Of this group the menopause had been normally established at an average age of 49.6 years in all but three patients. These had had an artificial menopause produced by intrauterine radiation at an average age of 48.3 years. In the post-menopausal group, the disease seemed to be associated with a late rather than an early menopause.

TABLE IV. RELATION TO MENOPAUSE AND PARITY

STATUS AND NUMBER		AVERAGE AGE	NULLIPAROUS 47.6%	PAROUS 52.4%
Premenopausal	20 47.6%	42.0 years	10	10
Postmenopausal	22 52.4%	60.3 years	10	12

In view of reports in the literature[9] in reference to malignancy developing in the fundus of the uterus subsequent to irradiation therapy for benign conditions, it is of interest to note that five of the patients had had previous irradiation. One of these would appear to have already developed sarcoma when radiated. Three of the remainder were given sterilizing doses of intrauterine irradiation to control bleeding at the menopause. These patients were 54, 51, and 40 years of age and developed the disease 10, 4, and 27 years later, respectively. The other was given radium at the age of 12 to control adolescent bleeding and developed sarcoma 21 years later. Correcting for the doubtful case, 9.3 per cent of the series had had irradiation prior to the development of the disease. This in no way supports or refutes the views expressed in the literature but it is thought provoking. One cannot overlook the experimental production of sarcoma by irradiation of inflamed tissues, as first done by Lacassagne[10] and later confirmed by Burrows and associates.[11] It is our opinion that there may be some inherent susceptibility to malignant disease in these individuals who require radiation therapy rather than any definite carcinogenic effect of the radium itself, and that the surgical removal of the bleeding menopausal uterus, in the light of increasing knowledge, may be more generally considered good prophylactic treatment in the future.

TABLE V. PATIENTS DEVELOPING SARCOMA OF UTERUS SUBSEQUENT TO INTRAUTERINE RADIUM THERAPY

CASE	AGE AT RADIATION	INDICATION	INTERVAL	TYPE OF SARCOMA
G 38	54 years	Menopause	10 years	Leiomyosarcoma
G 31	51 years	Menopause	4 years	Sarcoma in myoma
V 7	40 years	Menopause	27 years	Endometrial sarcoma
G 34	12 years	Adolescent bleeding	21 years	Endometrial sarcoma
V 26	66 years	Postmenopausal bleeding	6 months	Sarcoma in myoma

Histogenesis

The histogenesis of sarcoma of the uterus as now generally accepted by pathologists is that the tumor may arise from:

1. Muscle cells of the uterine wall.
2. Muscle cells of a myoma.
3. Connective tissue elements of the uterine wall, the intermuscular stroma.
4. Connective tissue elements of a myoma.
5. Stromal cell elements of endometrium.
6. Endothelium of blood vessels and lymphatics.

As these tissues arise from a common source, the embryonic mesoderm, it is possible to get a malignant connective-tissue tumor arising from any one of these elements or it may even show a mixture of their characteristics.[4] Sometimes a tumor arising in one type of tissue invades the field of another, making it difficult to define the exact site of origin.

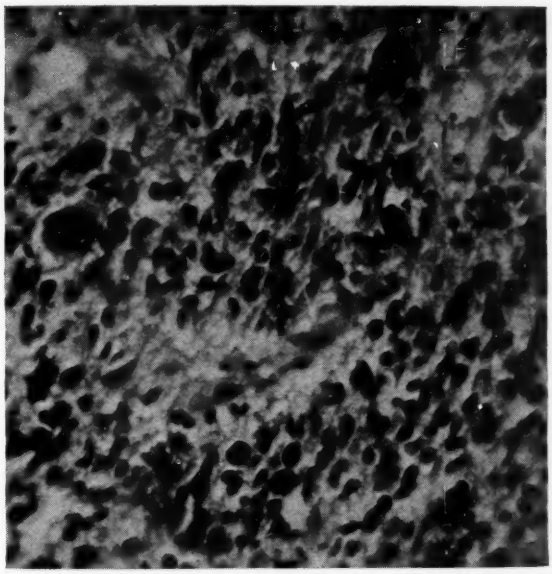

Fig. 1.—Highly malignant leiomyosarcoma in a myoma. Highly cellular pleomorphic tumor with many giant cells.

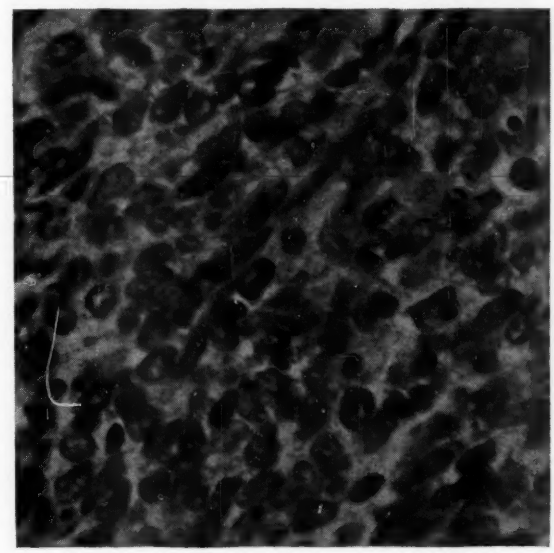

Fig. 2.—Mural type leiomyosarcoma. Highly anaplastic cellular tumor with many mitotic figures.

The myometrial tumors, whether in a myoma or the uterine wall, are for the most part leiomyosarcomas, but occasionally cannot be identified as muscle tumors and are thought to originate in the intermuscular connective tissue

stroma. These are considered by some to be identical with certain sarcomas of the tunica propria of the uterine mucosa.[12]

The endometrial tumors are particularly interesting, because of their relative rarity and frequently complex composition. They generally fall into three main types:

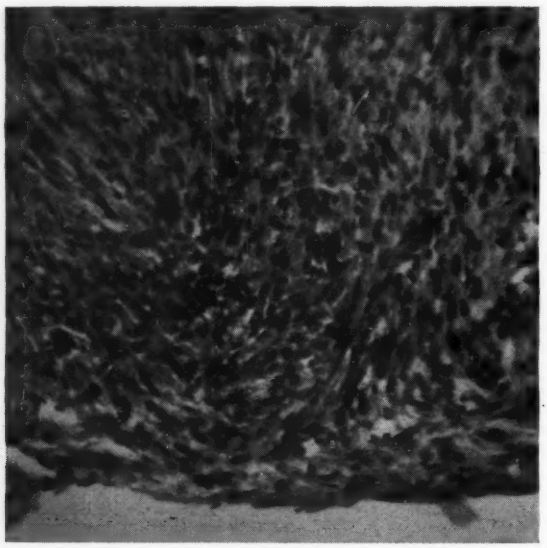

Fig. 3.—Type I endometrial sarcoma. Spindle- and anaplastic-cell tumor with scattered giant cells.

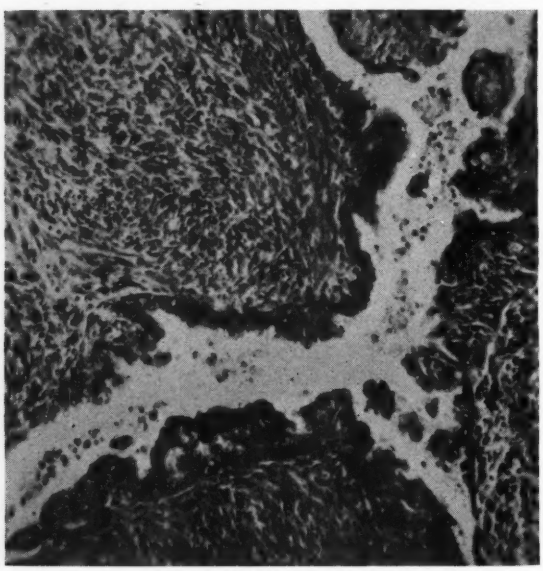

Fig. 4.—Type II endometrial sarcoma with carcinoma. Deep in sulcus of tumor, atypical heaped-up epithelium, carcinoma.

Type I.—These consist of sarcoma growing in a bulky bossellated fashion and, if not ulcerated, covered by a layer of normal columnar epithelium, which dips down between the bosselations. Endometrial glands are often incor-

porated. The stroma of the endometrium is simulated by small rounded or spindle cells in a diffuse, fine reticulum, or larger polygonal cells which resemble decidua. Myxofibrosarcoma with more or less abundant collagen may sometimes be diagnosed as arising in the endometrium.

Another more complex group consists of various mixtures of myxomatous tissue, fibrous tissue, cartilage, bone, fat, and muscle, often of embryonic striated variety, and are referred to as mixed mesodermal tumors of the uterus.

Some endometrial tumors, the rhabdomyosarcomas,[13 14] are said to be predominantly composed of striated muscle.

Type II.—This type consists of any of the variations of the previous type in which there is, in addition, adenocarcinoma within, but quite clearly demarcated from the sarcoma.[15, 16] These are frequently interpreted as separate tumors in accidental association.

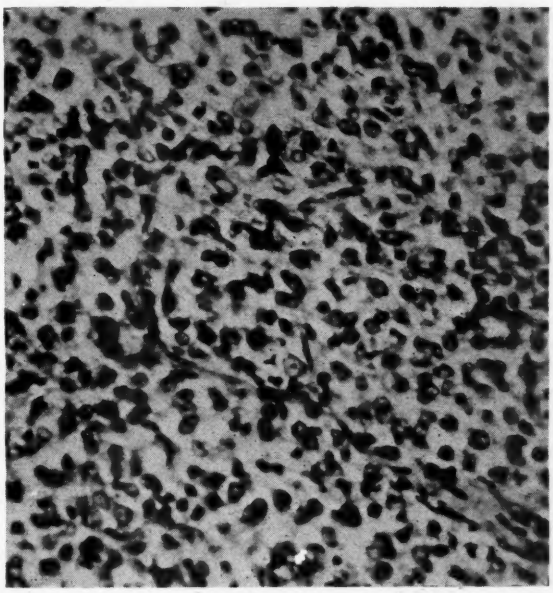

Fig. 5.—Type III endometrial carcinosarcoma. Diffuse, highly cellular sarcomatous area.

Type III.—This type consists of intimately mixed carcinoma and sarcoma with apparent transition from one into the other, the carcinosarcoma. Our interpretation is that this is an embryonal Müllerian malignant tumor in which both components of the endometrium may be represented, the stroma as sarcoma and the epithelium as adenocarcinoma. The latter probably develops from the primitive mesenchymal tissue of the sarcoma just as the epithelium from the mesenchyme in the genital ridge does in the genesis of the Müllerian duct. If we thus consider the whole endometrium as Müllerian, both the stroma and the epithelium normally become differentiated for a specific purpose. Each part, but particularly the stroma, is capable of reverting to its embryonal mesenchymal state and may appear as a myxosarcoma. Again, in its attempt to regenerate endometrium more fully, it may appear as an endometrial stromal cell sarcoma, or an endometrial carcinosarcoma.

By diversified or aberrant differentiation from this embryonal tissue, a mixed mesodermal tumor may develop, giving the various types of endometrial

sarcoma, such as myxofibrosarcoma, myxochondrosarcoma, myxoleiomyosarcoma, rhabdomyosarcoma, and others. A somewhat similar interpretation of these tumors has been suggested by Nicholson[17] and others.[18]

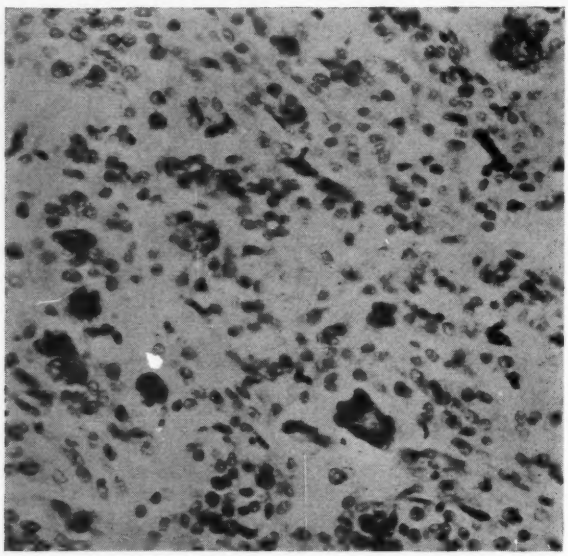

Fig. 6.—Type III endometrial carcinosarcoma. Additional small knots of cells of epithelial nature and early gland formation.

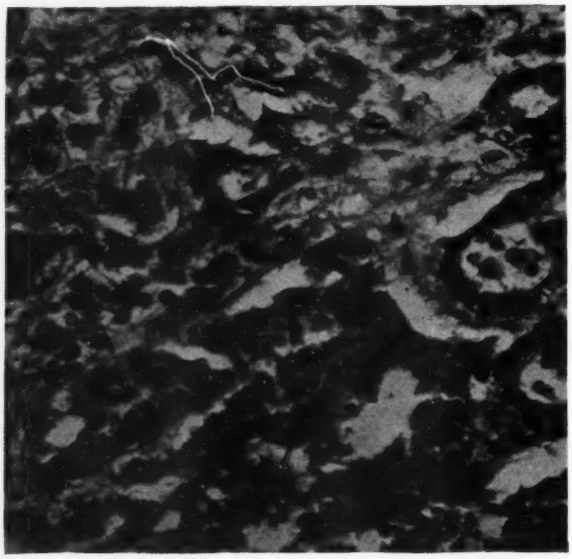

Fig. 7.—Type III carcinosarcoma. Adenocarcinoma, poorly defined above, well defined below, in a sarcomatous stroma.

Gross Diagnosis

Diagnosis is sometimes made at operation but more often it requires confirmation by microscopic examination before being definite. Grossly, the tumor is usually soft, succulent, and markedly vascular. The supporting tis-

sues, broad and round ligaments are often unusually friable. If the tumor arises in a fibroid there is frequently no clear line of demarcation between benign and malignant tissue, it being quite impossible to shell out the fibroid as is usual. The cut surface may appear homogeneous or necrotic and degenerated, the usual whorled appearance of the leiomyoma being lost. With the mural type it may begin as a fairly circumscribed nodule which on palpation may suggest a myoma. At times this may encroach on the cavity, simulating an endometrial origin. In one of the cases, No. 36, such a tumor filled the uterine cavity and appeared in the cervix and vaginal vault as an ulcerating, infiltrating, necrotic mass of tissue, an example of a tumor of one field invading that of another.

An endometrial sarcoma or a carcinosarcoma usually appears as a bulky polypoid intrauterine mass which sometimes fills the cavity. Most of these are well demarcated from the muscle and gross invasion of the myometrium is not easily determined but microscopically variable degrees of invasion are usually evident with penetration of lymphatic and blood vessels demonstrable. The involved muscle then becomes stretched over the bulk of the tumor.

Diagnosis by curettage is often disappointing and in one case was misleading. Frequently the removed tissue is so degenerated that the cellular structure is lost and its true character is not recognizable. Such a finding after curettage should be viewed with suspicion and demands repetition of the procedure. In one of our patients, as already mentioned, it was only on the third curettage that tissue suggesting sarcoma was found. Such a rapidly recurrent "polyp" should make one suspicious and justifies more radical procedures. In a second patient, with a case of postmenopausal bleeding, curettage revealed only atrophic endometrium and intrauterine radium was used, although it was recognized that a small fibroid was present. Only when reactivity as evidenced by rapid enlargement of the uterus was too obvious, was it belatedly removed—a sarcoma.

The finding of fibroid tumors of the uterus is so common that the surgeon is prone to become careless in his gross examination. Although the diagnosis must be finally made on histological and morphological evidence, careful examination of every fibroid removed at operation should be made. Each tumor should be exposed by cutting in the operating room, and, if any alteration in the usual appearance is noted, microscopic examination must be completed.

Types of Tumor

Many times the exact origin may only be conjectured, especially in the advanced case and thus classification as to origin can hardly be considered exact. Of the entire series, twenty-seven tumors (64.3 per cent) were considered to originate in pre-existing myomas although for obvious reasons certain of these might still be debatable. This represents a sarcomatous transformation of 0.52 per cent in the 5,165 myomas observed, and closely approximates the published statistics.[4, 8] The term "sarcomatous degeneration" is no longer used in describing these tumors. In thirty-two patients there was one or more coincident myoma so the mere presence of fibroids does not necessarily prove the origin of the sarcoma.

In four patients the tumor appeared to be a myosarcoma arising primarily in the uterine wall. Four patients had endometrial sarcoma of Type I described above. Three patients had endometrial carcinosarcoma, Type III, in which the sarcomatous and carcinomatous elements were intimately mixed and gave the impression of a transition one into the other. Three patients had sarcoma of the endometrium with small but distinct and separate areas

of carcinoma, two being definite adenocarcinoma of the fundus and one epidermoid in type. The latter arose in the cervix and might be considered as of the botryoides type. In one case untreated except for diagnostic curettage, it was impossible to determine the origin on histological examination.

TABLE VI. TYPES OF TUMOR IN 42 PATIENTS

TYPE	NUMBER	PER CENT
Sarcoma in myoma	27	64.3
Sarcoma primary uterine wall	4	9.5
Endometrial sarcoma	4	9.5
Carcinosarcoma	3	7.1
Sarcoma plus adenocarcinoma	2	4.7
Sarcoma plus epidermoid carcinoma	1	2.4
Sarcoma (indeterminate)	1	2.4

Frequently difficulty is experienced by the pathologist in the interpretation of histological findings, and the assessment of malignancy of these tumors. Among the many criteria of malignancy recorded, the tumors studied in this series were mainly diagnosed on the basis of their cellularity, pleomorphism, anaplasia, nuclear structure, mitotic figures, and invasiveness.

Individual mitosis counts were not done, as outlined by Evans[19] and others,[3, 4, 5] as there was considerable variation in the pathological technique employed and we felt that the methods were insufficiently standardized to allow for any accuracy. Variation in cell shape, often used as an index of malignancy, did not prove satisfactory in our hands. The variations in cell shape observed in different areas of the same tumor would seem to invalidate this method of judging the malignancy in many instances, while in others it was an aid in assessing the general picture.

Six of the tumors were diagnosed as leiomyosarcomas of low grade. These all arose in myomas. In each case there was sufficient histological evidence of malignancy to preclude a pathological diagnosis of a benign tumor although the pathologist noted that these tumors were of low-grade malignancy. Some had frequent mitoses, evidence of invasion, and some pleomorphism. Five of these patients are alive and well, three of them surviving for over ten years. One of this group died of pulmonary embolus during the postoperative period.

Symptomatology

The symptomatology of the disease is unfortunately not diagnostic, especially in the younger premenopausal group. In these the signs and symptoms, menorrhagia and an enlarging abdomen, closely follow those of a simple fibroid. An abdominal tumor which has appeared quickly and seems to be actively growing is suggestive. A rapidly enlarging fibroidlike tumor should be viewed with suspicion at any age but in the postmenopausal group it is of particular significance. Menorrhagia and metrorrhagia were predominant symptoms in 73.8 per cent of patients. In fifteen patients, 35.7 per cent, bleeding was of postmenopausal timing. Abdominal-pelvic pain occurred in 60 per cent of the patients but it was not an early symptom. Fetid leucorrhea, pressure effects, and loss of weight were each present in more than 30 per cent of the patients. It is interesting to note that fourteen patients were febrile on admission. This undoubtedly is an important sign, as these tumors are so frequently the site of active inflammation or advanced necrosis and degeneration.

In one patient, a 29-year-old virgin, the breasts were actively lactating. The tumor mass was about the size of a seven-month pregnancy and proved

to be a sarcoma arising in a pre-existing myoma of the uterus. It was highly malignant in histological appearance and the patient died of recurrence six months after hysterectomy. To our knowledge, lactation has not been previously recorded in association with sarcoma of the uterus.

TABLE VII. SYMPTOMATOLOGY

SYMPTOM	NUMBER OF CASES	PER CENT
Menorrhagia or metrorrhagia	31	73.8
Pelvic or abdominal pain	25	59.5
Pelvic mass	23	54.7
Frequency and nocturia	19	45.2
Pressure	14	33.3
Loss of weight	15	35.7
Fever	14	33.3
Constipation (increasing)	13	30.9
Lactation (virginal)	1	2.4

Treatment

The methods of treatment used were:

1. Radiation by intrauterine radium.
2. Surgical removal alone. (Both total and subtotal hysterectomy with and without salpingo-oophorectomy.)
3. Surgical removal preceded or followed by deep x-ray therapy.

The varied forms of treatment given these patients can be attributed to several factors. The predominant reasons seem to be the natural variation in methods over a twenty-year period, the fact that two hospitals and twenty individual surgeons are involved in the series, the difficulty in diagnosis or the careless gross examination of removed specimens, and the inadequacy of individual experience with this disease. Even in earlier years, when subtotal hysterectomy was a more frequent operation, those cases thus treated usually resulted from the failure, on the part of the surgeon, to recognize the true character of the disease. Often these patients were given deep x-ray therapy as an adjunct to what probably was considered inadequate surgical treatment.

In a few cases deep roentgen therapy was given preoperatively in an effort to control the spread of disease in what appeared to be a hopeless case. In two instances there was such marked improvement that surgical removal was considered feasible and was then done with encouraging although perhaps not curative results, insufficient time having elapsed since operation to judge. As pointed out by Randall,[20] the effectiveness of irradiation preoperatively on highly cellular endometrial sarcomas may be of palliative benefit.

The six patients who were treated by radium alone all died, one living four years without recurrence. This must be considered in the light of the fact that four of these tumors were endometrial in origin and one arose in the wall. These types are generally considered more malignant than those arising in a myoma but from this small experience radiation alone would not seem to be satisfactory.

Twenty-two patients were treated by surgery alone. Thirteen (59 per cent) of these succumbed, two in the postoperative period and eleven from recurrence or metastases. In ten of those with fatal outcome, the tumors had developed in myomas, showing that sarcomatous transformation of a myoma, even when removed, is by no means harmless.

Thirteen patients were treated by surgery, with deep x-ray therapy either pre- or postoperatively. Seven (53.8 per cent) of these patients have died, four of whom had sarcomatous change in a myoma.

From this small series it is difficult to be dogmatic, but it would appear that surgery with postoperative roentgen therapy is so far the management of choice.

No patient in this series or in any other in the literature, to our knowledge, was subjected to a more radical procedure than ordinary total hysterectomy. White and co-workers[21] recommend Wertheim hysterectomy followed by deep x-ray therapy in cases of sarcoma if the cervix is involved. If the diagnosis could be confirmed at operation, a radical hysterectomy with gland removal should certainly be considered, as the spread of this disease is so often by local extension and lymphatics. Only two cases in our series came to autopsy. Both had no distant metastases, but most extensive local recurrence filling the pelvis and involving the adjacent organs by direct extension. In several of the other cases observed during the final illness the main evidence of recurrence was in the lower abdomen or pelvis. It would seem logical that a more extensive primary dissection with removal of the parametrium and lymphatic areas of drainage might have improved our results.

Follow-Up Study

For the purpose of follow-up studies the patients were divided into two groups. The first group of twenty-seven patients was composed of those treated up to 1944, in whom a five-year review was possible. The second group of fifteen patients were treated since 1944. In reality the first group became a ten-year follow-up as all those treated from 1939 to 1944 were already dead.

The operative mortality for the entire series occurred in the first group. There were three patients who died postoperatively. This made an immediate mortality of 11.1 per cent (7.1 per cent for the entire series). Two patients died during the early postoperative period, one of pulmonary embolism on the tenth day, and the other, moribund on admission, on the second postoperative day, from generalized peritonitis secondary to widespread sarcomatosis. One patient was not treated except for diagnostic curettage which revealed leiomyosarcoma of indeterminate origin, filling the uterus, cervix, and vaginal vault. Treatment was refused and she died at home two weeks later, but the case is included as further treatment could hardly have affected the outcome. Of the twenty-four patients remaining in the first group, eight (29.6 per cent) were alive and well for five years, six (22.2 per cent) were alive and well for ten years. Three patients were alive but with recurrence at five years. These all died in the sixth year. One additional patient had suffered recurrence but was alive at the tenth year, succumbing eleven years after treatment. The five-year mortality was thus 60 per cent, and the ten-year mortality 74 per cent. This emphasizes the contention that late recurrence of these tumors is quite possible and that it is a deadly disease.

Of the second group of patients, fifteen in number treated since 1944, there was no operative mortality, four patients died in the first year, one in the second, and one in the third year. Two patients are alive with recurrence and six patients are alive and well from one to four years. Already after an average follow-up of two and one-half years, 53.3 per cent of the patients are either dead or with recurrence and 46.6 per cent alive and apparently well.

Considering recent efforts to educate the public to report abnormal symptoms to their physicians promptly, a correlation of the duration of symptoms before admission with the ultimate outcome of the disease was studied. With such a rapidly progressing disease the results of early diagnosis are disappointing but for the most part prompt diagnosis and treatment would appear

to be a factor in prognosis. The extreme difficulty in making a clinical diagnosis remains the greatest problem. Forty-three per cent of the patients who had had symptoms for two months or less died, while 83.1 per cent of the patients with symptoms from three to twelve months' duration succumbed.

TABLE VIII. FOLLOW-UP STUDY ON 42 CASES OF UTERINE SARCOMA

STATUS	INTERVAL	NUMBER	PER CENT
Group 1. 27 cases, 1929-1944.—			
Alive and well	5 years	8	29.6
	10 years	6	22.2
Alive with recurrence	5 years	3	11.1
	10 years	1	3.7
Operative mortality		3	11.1
Died, recurrence or metastases	1st year	9	33.3
	2nd year	2	7.4
	3rd year	1	3.7
	4th year	1	3.7
	6th year	3	11.1
	10th year	1	3.7
	11th year	1	3.7
Group 2. 15 cases, 1944-1949.—			
Alive and well	1 year	4	
	3 years	2	46.6
	4 years	1	
Alive with recurrence	1 month	1	13.3
	9 months	1	
Operative mortality		0	0
	1st year	4	
Died, recurrence or metastases	2nd year	1	40.0
	3rd year	1	

Conclusions

1. A statistical, clinical, and pathological review of forty-two cases of uterine sarcoma covering a twenty-year period, is presented.

2. A five-year cure rate of 29.6 per cent and a ten-year cure rate of 22.2 per cent are recorded.

3. Clinical diagnosis is so seldom made that improved diagnosis at operation is imperative.

4. Careful examination of every fibroid removed should be a routine.

5. Sarcoma of the uterus is usually a lethal disease, although it may exhibit variable degrees of malignancy.

6. Surgical removal with postoperative deep roentgen therapy is the accepted treatment but more radical surgical removal is suggested.

I wish to express my appreciation to Drs. J. S. Pritchard and J. P. A. Latour for their invaluable assistance with the pathological studies in the preparation of this paper.

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Discussion

DR. CLYDE L. RANDALL, Buffalo, N. Y.—Since the histologic diagnosis must exclude borderline tumors with atypical cellularity, it is not surprising that the reported incidence varies and that even the malignant character of this tumor is occasionally questioned.

On the basis of follow-up studies reported in 1942 from the Buffalo General Hospital, I would agree with Dr. MacFarlane that fibriods showing atypical cellularity should be excluded from a review of uterine sarcomas. Atypical cells *and* mitotic figures together have rarely been reported in tumors considered benign by our pathologist, but atypical cells *or* mitotic figures have been recorded four times more frequently than sarcomas of the uterus. We are maintaining a follow-up study on sixty-two patients whose removed myomas revealed atypical cellularity. Twenty-two of the group have been followed for more than five years (eleven for more than ten years), two are dead, one with an acute purpura and a subarachnoid hemorrhage eight months after hysterectomy, one with hypertensive cardiovascular disease and an intracranial hemorrhage eleven years after operation. Not a single tumor considered an atypical fibroid has, to date, shown anything to suggest malignancy.

The incidence of sarcoma we have observed somewhat parallels Dr. MacFarlane's experience. He reports one sarcoma per 123 benign myomas. Our records show one sarcoma per 106 fibroids (51 sarcomas, 5,424 fibroids). He found sarcoma to comprise 2.53 per cent of uterine malignancies. In the State of New York the Division of Cancer Control reports that slightly more than 2 per cent of uterine malignancies are sarcoma. The proportion of sarcomas apparently arising in myomas (64.3 per cent in Dr. MacFarlane's series) seems high; at least in our material only 28.6 per cent of sarcomas have been associated with fibroids. I believe this point is important. If we want to estimate prognosis and think in terms of curability, we must distinguish between so-called secondary sarcoma, and primary sarcoma developing without appreciable relationship to a myoma. Whether we accept or reject the concept of sarcomatous degeneration in myomas, sarcomas developing in a fibroid prove relatively benign. We might report that 34 per cent of the women with uterine tumors considered sarcoma at the Buffalo General Hospital are surviving five plus years—but I believe such figures are misleading. At least it seems more practical to note that when the sarcoma has been found incidentally in a uterus removed because of fibroids, 75 per cent of such patients show no evidence of a malignant tumor five or more years after hysterectomy. On the other hand, when curettage or hysterectomy was indicated for bleeding and sarcoma was found unassociated with fibroids, less than 15 per cent of such patients have survived five years.

In his material Dr. MacFarlane has recognized various histologic types of sarcoma. I would like to know if he found evidence that the histologic type seems to influence the prognosis. When based only on material obtained by biopsy or curettage, Dr. MacFarlane says the diagnosis was "judged to be unsubstantiated." Are we to understand that in all cases the diagnosis was based on examination of the removed uterus, or were some cases of endometrial sarcomas and sarcomatous polyps included even though a hysterectomy was not performed?

Gross sectioning of myomatous uteri at the operating table in an effort to recognize sarcoma at that time has been repeatedly advised. Dr. MacFarlane suggests that excision more adequate than the standard total hysterectomy should be employed until the effectiveness of more radical surgery can be evaluated. I would like to ask if, in the material reviewed, he has been able to correlate the extent or completeness of operative removal and the length of time the patient survives?

We have also noted unexplained fever in large tumors proved to be sarcomas at operation. We have also been impressed by the sinister import of rapidly recurring cellular but benign fibroid "polyps." The clinical diagnosis is difficult and the importance of appreciable enlargement of an apparently benign myoma *after the menopause* has been frequently emphasized. However, since sarcomas are relatively rare and we have occasionally noted the postmenopausal growth of benign fibroids, I would like to ask if Dr. MacFarlane has attempted to estimate how many of the clinically myomatous tumors that grow after the menopause proved to be sarcoma at operation.

DR. HERBERT E. SCHMITZ, Chicago, Ill.—Although uterine sarcoma is rare, it is highly fatal unless discovered early and treated by complete removal of the uterus and adnexa. Early diagnosis is difficult because the symptoms are not always characteristic and are also common in association with fibromyomas. Immediate examination of the removed specimen before closure of the abdomen is unfortunately not routine with all surgeons. As a consequence, a high percentage of patients being referred for irradiation therapy have had incomplete surgical attention. If total hysterectomy were a more common procedure more of these women would be salvaged, for x-ray or radium therapy is woefully inadequate treatment for uterine sarcoma.

The histologic classification of sarcoma based on the undifferentiated mesenchymal cell, namely, round-cell, spindle-cell, or mixed-cell varieties, should be replaced by one which gives the origin of the growth whenever possible; namely, leiomyosarcoma, fibrosarcoma, endometrial sarcoma, and using the classification of undifferentiated sarcoma for those tumors of which the tissue of origin is not clear. If we accept this latter classification we may then proceed to establish their resistance or sensitivity to irradiation according to the degree of differentiation and undifferentiation.

The unripe blastomas are composed of either small round cells or small spindle cells of low differentiation or high degree of anaplasia. They are clinically very malignant, form metastases early and freely, and are radiation sensitive. The cells of middle ripe sarcoma have attained a certain degree of differentiation. They are fibrosarcomas and myxosarcomas. The sarcomas occurring in myomas belong in this group which comprises the largest number of connective tissue tumors of the uterus. They are clinically less malignant and rarely form metastases. The ripe connective tissue tumors are myofibromas. They are mostly composed of relatively fully differentiated, spindle-shaped smooth-muscle cells and ripe connective-tissue fibers. They are clinically benign.

The status of the carcinosarcoma is a questionable one. It is thought not to be a collision of two separate tumors but rather a tumor in which spindle-shaped elements are intimately intermingled with more or less typical epithelial cells. It is exceedingly difficult in many instances to state whether both stroma and epithelium have assumed malignant properties, or whether the epithelial cells have merely become spindle shaped.

Sarcoma botryoides is a round-cell sarcoma in which embryonic elements are sometimes found. The round cells are undifferentiated elements, hence to call these mixed tumors of the cervix would be more exact and descriptive.

The high incidence of sarcoma reported occurring in uteri previously irradiated for supposed benign disease is startling. Sarcomas occurring in myomas are fibrosarcomas and myxosarcomas and comprise the largest group of connective-tissue tumors of the uterus. Novak believes that this fact is responsible for the rare occurrence of sarcoma in previously irradiated myomatous uteri. He suggests that the sarcoma is destroyed in most instances. Two patients in our series, who were treated for far-advanced squamous-cell carcinoma of the cervix developed myxosarcoma ten and twelve years later. In the interim, numerous courses

of x-ray therapy had been administered through many ports in an attempt to control the original disease. Tissue damage was extensive and the final process seemed to be one of necrosis and slough due to the irradiation. Microscopic examination of the tissues of the genital tract removed at autopsy failed to reveal any remnant of the epithelial new growth but extensive invasion of the vagina, uterus, and pelvis by the sarcoma. It is my opinion that the over-irradiation was a factor in producing this change. Sarcoma has not been seen in our clinic following irradiation for benign menopausal bleeding, although this is the procedure of choice in the treatment of such bleeding. One patient so reported must have had the disease when first treated five years previously because her bleeding recurred on four occasions at which time she was given further radium therapy. It is our policy never to reirradiate a uterus for benign disease if the first dose was considered adequate but failed to arrest the bleeding. In most instances the true diagnosis of sarcoma, adenocarcinoma of the Fallopian tube, early endometrial carcinoma not accessible to the curette, or ovarian tumors has been overlooked.

DR. FRANK R. SMITH, New York, N. Y.—It is very difficult to get pathologists to agree as to what sarcoma is. Consequently it is very difficult to get comparable series from any hospital. At Memorial Hospital in New York, we have had 47 patients with undisputed sarcoma. There has been agreement by two, and in most instances three, pathologists in that group. There are 39 patients who are dead. In the group that died, four lived four years but none lived five years. In the group that is alive, numbering eight, five are alive less than three years. One is alive four years but will soon be dead; one is alive six years and was lost track of this past year. She may very probbaly be dead, although she was free from disease at that time, but a review of her slide now clarifies that her sarcoma was the mixed mesodermal type. The one patient who lived any length of time (twelve years) had a very low-grade type of endometrial sarcoma and incidentally was treated elsewhere by supracervical hysterectomy and very inadequate doses of irradiation afterward. Most of these patients at Memorial have been operated upon elsewhere. Of twelve patients, six had recurrences in the cervix. At Memorial they have been treated extensively with x-ray with the 250,000 volt machine and many of the latter group with the million volt machine. Also, various types of radium applicators have been used. I have seen in no instance a beneficial result with irradiation in sarcoma. In connection with one point that Dr. MacFarlane brought out, relating to patients who have been previously irradiated for benign lesions, we reviewed over 1,000 patients with benign lesions who had been followed eight to twenty years following irradiation and while we found 30 to 35 patients who later developed carcinoma, there was only one patient in this series who later developed sarcoma.

DR. A. D. CAMPBELL, Montreal, P. Q.—This presentation vividly reminds us that this deadly tumor so often masquerades in the guise of a benign fibroid.

May I cite a case? A woman doctor, aged 46 years, had been examined routinely annually for the past twelve years or more; the pelvic findings were always none other than that of a small fibroid in the posterior wall of the uterus, half the size of an English walnut. As late as the fall of 1948, she was apparently well, and apart from a slight tenderness of the fibroid, nothing could be elicited. In January, 1949, she consulted her internist for persistent fever and general malaise. No cause could be found for this constant temperature of 102 to 103° F. In April, 1949, when I was asked to see her, I found an ill-defined mass filling the cul-de-sac, which suggested endometriosis. In spite of the temperature, I recommended a laparotomy which was performed late in April of this year.

At the time of operation, both ovaries were found high in the pelvis and enlarged to the size of small oranges, containing a considerable amount of chocolate material, which later proved to be endometriosis. The cul-de-sac was filled with a semisolid, grayish, necrotic mass which seemed to rise from the posterior wall of the uterus. All the pelvic organs were removed. Histological examination of the findings showed bilateral endometriosis. The mass was diagnosed histologically as carcinosarcoma. Pathologists both in Boston and in Montreal agreed.

It is interesting to note that the endometrium was perfectly normal and intact. Deep x-ray therapy was instituted but proved ineffective. The patient continued to run a fever. Gradually becoming more emaciated, she died of pneumonia some three months later. At autopsy, only a few small secondary growths were detected in the liver and in the lungs.

The lesson to be learned from this case is that carcinosarcoma or sarcoma of the uterus, as Dr. MacFarlane pointed out, may for years masquerade as a benign fibroid. One cannot recommend total hysterectomy for every small symptomless fibroid, but we should take more serious cognizance of those that become tender. Further, our prognosis preoperatively should be more guarded when we are consulted on the probable prognosis of a given tumor clinically regarded as a fibroid.

DR. EMIL NOVAK, Baltimore, Md.—Several of the speakers have called attention to the importance of cutting into uterine myomas immediately after removal and before closing the abdomen, and this point deserves underscoring. If the cut surface is hard, glistening, and trabeculated in the characteristic whorllike fashion, one does not need to worry about sarcomatous degeneration. If the surface is rather soft and homogeneous in certain areas, and of rather glassy appearance, the tumor is probably the seat of extensive hyaline degeneration, which is often combined with cavities produced by cystic change. On the other hand, if the surface is soft, pulpy, and pultaceous, with often ragged cavities produced by necrosis, sarcoma should be suspected and the extent of the operative procedure be influenced accordingly.

Curettage is not likely to yield evidence of sarcoma except in the endometrial and endocervical varieties, and perhaps occasionally in a submucous growth. It should be remembered that both endometrial and endocervical sarcomas have a tendency toward polypoid architecture. I have more than once examined sections of supposedly simple cervical polyps which were found to be sarcomatous, and later curettage in such cases often yields abundant sarcomatous tissue. The sarcomatous polyp is usually bulkier and more infiltrated than the characteristically fragile and friable ordinary cervical polyp.

A good many postoperative headaches are suffered by surgeons who are not pathology minded. For example, a subtotal hysterectomy is done for myoma, and several days later the pathologist reports, sarcomatous change in the uterus. What to do? Shall the surgeon go back and do a radical operation, or shall he resort to irradiation? Each case must be decided individually. In sarcomatous myomas of a low degree of histological malignancy, where the level of amputation has been well below the tumor, I believe there is no hazard in avoiding further operation, as well as irradiation if the patient is young. Under other conditions, secondary and more radical operation and /or irradiation will be the wiser plan. As a group, the sarcomas arising in myomas are less malignant than those of diffuse intramural variety, but there are not a few exceptions. The relatively lower malignancy of sarcoma arising in myoma is due in part to intrinsic characteristics, but probably in part also to pathologic misinterpretation, as very cellular but benign myomas are often wrongly diagnosed as sarcoma.

Finally, a word as to carcinosarcoma, which can undoubtedly occur. On the other hand, my experience has been that not a few cases in which this diagnosis has been made are adenocarcinomas of very infiltrating type and not instances of combination tumors. Many unquestioned adenocarcinomas show little or no evidence of such histologic criteria of invasiveness as penetration of the basement membrane or penetration into the lymphatics. In some, however, the break-through is obvious and extreme, cancer cells infiltrating the stroma and often simulating the picture of associated sarcoma.

Finally, I note that the essayist did not include in his discussion the so-called malignant stromatosis, a relatively rare lesion which represents the malignant prototype of stromal adenomyosis or benign stromatosis. I believe that the malignant form is to be looked upon as only a variant of endometrial sarcoma.

DR. MacFARLANE (Closing).—In reply to Dr. Randall, I am quite in agreement that generally speaking a sarcoma found in a myoma is less malignant than that occurring as a

primary growth but I do not believe that this can be used in every case as a guide to treatment or prognosis. As Dr. Novak has said, there are exceptions and careful histological studies are our only means of identification.

As to the influence on prognosis of various histological types we did not use the old "cell shape" classification but we found that the prognosis was most closely associated with the degree of cellular immaturity or differentiation, as pointed out by Dr. Schmitz.

I believe Dr. Randall must have misinterpreted my statement about material obtained on curettage and biopsy. In two cases the amount of tissue obtained was really insufficient on which to base a diagnosis and although these cases were in the hospital records, they were not included in the report.

Unfortunately, in our series, a good many cases were treated by subtotal hysterectomy, with or without removal of the ovaries, and immediately given x-ray therapy which influences the result and makes it difficult to correlate the type of removal and prognosis. Our best results were in those cases subjected to total hysterectomy and bilateral removal of the ovaries.

In regard to Dr. Novak's remark about malignant stromatosis, two of our cases had previously been reported by the late Dr. Goodall. Although considered benign at that time, the patients subsequently died of the disease. I feel as Dr. Novak does, that they should be considered another form of endometrial sarcoma.

THE MANAGEMENT OF EXCESSIVE FLUID RETENTION IN NORMAL AND TOXEMIC PREGNANCIES*

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A STATE of positive water balance is a normal accompaniment of pregnancy and is evidenced by an increase both in plasma volume and in extravascular fluid.[1] This phenomenon may be exaggerated to a point at which edema without any other demonstrable abnormality appears but a few patients develop pre-eclampsia in which the extravascular fluid retention is further exaggerated and with which the increased blood pressure and the appearance of proteinuria indicate a definite alteration in the physiology of the vascular system. Chesley states that the patient who retains fluid in excess of the normal is six times as likely to develop pre-eclampsia as is the one who retains only the normal amount.[2]

The reasons for the extravasation of fluid from the vascular system with its accumulation in the interstitial spaces are multiple but for the normally pregnant patient little evidence can be presented that more than a small minority fall into the following groups:

A. Reduced Oncotic Pressure Due to Decreased Plasma Proteins.—
Some maintain that dietary deficiencies are responsible for fluid retention during pregnancy as well as for pre-eclampsia but the majority of studies of both normal and toxemic patients indicate that with few exceptions the protein levels are well above the minimum necessary to prevent fluid leakage from the blood stream. It is well, however, before initiating treatment to determine the level of the plasma proteins for if they are significantly reduced edema can be corrected only by improving the nutritional state.

B. Increased Venous Pressure and Stasis.—
If the venous and capillary pressures are increased over that in the tissues the normal mechanism of fluid exchange may be altered with an increase in the tendency of water to leave the vascular system. In both normal and toxemic pregnancies the venous pressure is unchanged, except in the lower extremities,[3] while fluid accumulation in each is universally distributed over the entire body.

C. Abnormal Renal Function.—
With the possible exception of an altered uric acid excretion in pre-eclampsia there is no demonstrable change in renal physiology either in the early stages of this condition or in the normal patient with edema.

A logical explanation, since this phenomenon is universal in normal pregnancy and absent in the normal nonpregnant woman, is to be sought in a physiological change common to all pregnancies. As emphasized by Taylor, Warner, and Welsh,[4] there is during pregnancy a high level of steroid hormones which

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are capable of delaying the excretion of electrolytes and of the water necessary to maintain them in a suitable tissue concentration, thus providing an obvious cause for the hydremia of normal pregnancy and at least in part for its exaggerated state in pre-eclampsia. They were able to produce a definite delay in both sodium and water excretion in normal and toxemic puerperal patients by the administration of sufficient quantities of estrogens and progesterone. In a previous study[5] they had noted that sodium loss and the associated postpartum diuresis began only after termination of placental function as indicated by cessation of the urinary excretion of estrogen and pregnandiol. More recently, Tobian[6] has demonstrated a marked increase in excretion of corticosteroids in pregnant women with edema or pre-eclampsia as compared with normal pregnant women. Excretion of these substances in the latter was twice that of nongravid women.

The earliest clinical sign of developing pre-eclampsia is an increased retention of water which may be evidenced only by an abnormal increase in weight. It is at this stage that intensive therapy directed toward reversing the flow of fluid may be effective in preventing advance of the condition. Although there is general agreement that fluid retention is an early sign of pre-eclampsia and that its treatment is important, opinion differs as to the method by which it can be mobilized most effectively. We have in this study attempted to contrast and to evaluate two methods of dehydration which are opposed to each other in rationale but which are widely used for the treatment of pre-eclampsia.

Method

Nineteen edematous patients between the thirtieth and fortieth weeks of pregnancy were studied. Of these, eleven were primigravidas and eight were multiparas; ten were normal, and in nine a diagnosis of pre-eclampsia was made. All had been followed in our prenatal clinic and before admittance to the hospital an attempt had been made to control the fluid retention by outpatient therapy consisting of instruction in the preparation and use of a low-salt diet without limitation of fluids. In all the weight and edema increased despite repeated interviews and reinstruction; thus only patients whose fluid imbalance could not easily be corrected are included. Edema in these patients was graded as plus one in eight, plus two in six, and plus three in five.

After admittance to the hospital the patients were maintained on a standard diet containing less than 2 Gm. of sodium chloride and 85 Gm. protein daily and during the control period of two to four days the following studies were carried out: daily weights, daily determinations of hematocrit and blood protein, measurement of fluid intake and output with an analysis of the twenty-four hour urine chloride and protein excretions. Following the control period each patient was dehydrated by one of two methods, no attempt being made to select patients for either group.

A modification of the classical technique suggested by Arnold and Fay[7] was utilized for one group of nine patients of whom four were normal and five had pre-eclampsia. These patients were given 60 c.c. of a saturated solution of magnesium sulfate by mouth four times over a twenty-four hour period or 60 c.c. twice daily for three or four days. Fluid intake was limited, in almost all instances being less than 300 c.c.; in only two was it over 500 c.c., the highest being 720 c.c. in any twenty-four hour period. Nothing except the medication and small amounts of fluid were taken by those dehydrated for the short period; a

dry diet was ordered if more prolonged dehydration was planned. Although the dehydration in this group was more severe than is usually prescribed for simple fluid retention, it is comparable to the regimen suggested for the treatment of pre-eclampsia and was chosen to compare with the other method of dehydration which also is an important part of a therapeutic regimen for toxemia.

The second group of ten patients, including six normal and four with pre-eclampsia, were placed on an acid-ash salt-poor diet (less than 400 mg. sodium chloride), approximately 2,000 c.c. of fluid daily, and ammonium chloride 3 Gm. three times daily by mouth over a five-day period.

During the study period each patient was confined to bed and was weighed daily at the same time, and the hematocrit and blood proteins were checked twice daily except during the period of acute dehydration with magnesium sulfate when they were checked four times during each twenty-four hour period. A record was kept of fluid intake and output from all sources except insensible loss which was impossible to measure. In order to obtain some information concerning electrolyte excretion, the total chlorides excreted in the urine and the diarrheal stools were calculated for each twenty-four hour period; all formed stools were not checked for chloride because so little was lost by this route that it seemed impractical. At the completion of the study period each patient was returned to the control regimen for the remainder of the period of observation.

Results

Because of the extreme variability in the conditions of the patients and the distinct difference in the methods used for the mobilization of fluid, it is difficult to make an accurate percentage comparison of the results from each method of therapy. Certain major differences are outstanding and these will be discussed and illustrated with typical cases.

Weight Loss.—

During the initial control period, while all patients were on a low-salt diet with adequate fluid intake, there was a weight loss which averaged 4 per cent of the admittance weight for those who ultimately were given magnesium sulfate and 3.5 per cent for the ammonium chloride group. Because of this the changes after institution of therapy were somewhat less striking than they would have been had the experimental conditions been instituted earlier.

TABLE I. WEIGHT LOSS WITH FLUID LIMITATION AND MAGNESIUM SULFATE PURGATION

PATIENT NO. 1, AGED 27 YEARS, GRAVIDA V, PARA IV, 40 WEEKS. TOXEMIA

DAY	WEIGHT (POUNDS)	FLUID			TREATMENT
		INTAKE (C.C.)	URINE (C.C.)	STOOL (C.C.)	
1	203	720	1,800		Salt-poor diet (less than 2 Gm. NA CL)
2	200	900	1,325		
3	198¼	1,070	1,100		
4	198¼	240	225	2,400	Magnesium sulfate 60 c.c. saturated solution, 4 doses
5	186¼	240	300		
6	192	1,440	600		Salt-poor diet
7	192	900	1,450		

Magnesium sulfate administered by mouth was followed by a rapid decrease in weight due to fluid loss (Table I). The greatest loss in any twenty-four hour period of purgation was twelve pounds and the smallest three and one-half. After the drug was stopped despite the fact that a low salt intake was continued there frequently occurred an increase in weight as fluid returned to the blood

and extravascular spaces. This weight rebound was less evident or absent if purgation was extended over periods of time longer than twenty-four hours (Table II).

TABLE II. FOUR-DAY FLUID LIMITATION AND MAGNESIUM SULFATE PURGATION

PATIENT NO. 7, AGED 23 YEARS, GRAVIDA II, PARA I, 38 WEEKS								
		FLUID			URINE	STOOL	PLASMA	
DAY	WEIGHT (POUNDS)	INTAKE (C.C.)	URINE (C.C.)	STOOL (C.C.)	CL (GM)	CL (GM)	PROTEIN (GM)	TREATMENT
1	175	1,020	2,775					Low-salt house
2	170	1,140	3,330		4.8		6.5	diet
3		1,865	2,360					
4	164¾	1,680	1,985		5.3		6.1	
5	163¾	480	370	1,760	0.8	1.5	7.8	Dry diet, mag-
6	159½	720	360	1,434	1.5	1.4	8.2	nesium sulfate
7	156¾	360	270	1,755	0.9		8.0	60 c.c. b.i.d.
8	154¾	270	400	830	0.13		7.8	
9	154½	1,800	810		0.13		8.2	Low-salt house
10	155½	2,880	1,810		0.84			diet
11	155½	3,240	1,505		0.8			
12	156	2,700	1,860				7.0	

On the acid-ash salt-poor diet and ammonium chloride the weight continued to decrease from that of the last control day but the immediate change was much less spectacular. The greatest weight loss in any twenty-four hour period was four pounds and the usual time at which the most rapid decrease began was during the second and third days of therapy rather than the first (Table III). In none of these patients was there noted an increase in weight after the treatment period.

TABLE III. WEIGHT LOSS, FLUID INTAKE, AND URINE OUTPUT WITH ACID-ASH DIET AND AMMONIUM CHLORIDE

PATIENT NO. 15, AGED 22 YEARS, GRAVIDA I, PARA 0, 36 WEEKS. PRE-ECLAMPSIA				
		FLUID		
DAY	WEIGHT (POUNDS)	INTAKE (C.C.)	URINE (C.C.)	TREATMENT
1	141			Salt-poor diet (less than 2 Gm.
2	139	2,340	2,515	NA CL.)
3	138¼	2,000	3,660	
4	138	2,780	2,700	Acid-ash salt-free diet (less
5	135¾	3,440	3,255	than 400 mg. NA CL)
6	134¾	2,160	3,900	
7	131	2,580	2,840	Ammonium chloride, 3 Gm. t.i.d.
8	129¾	2,200		Labor induced

Blood Volume.—

With magnesium sulfate dehydration there occurred a uniform decrease in blood volume as evidenced by an increase in hematocrit and plasma proteins (Table IV). The degree of change varied with the rapidity and amount of weight change; the greater and more rapid the fluid loss the more pronounced the hemoconcentration. With longer periods of dehydration the hemoconcentration persisted until the fluid intake was increased and the tissues were rehydrated (Table II).

In no instance was there any appreciable alteration in hematocrit or serum proteins in the patients who were not actively dehydrated by magnesium sulfate.

Urine Volume and Chloride Excretion.—

The urine volumes during the control period were uniformly high, the greatest output being 5,130 c.c. in one day. In only two patients did they fall

below 1,500 c.c., and in almost every instance the output exceeded the fluid intake. In all patients the initial urine chlorides were high, indicating a failure to have reduced the salt intake sufficiently at home, but the excretion fell rapidly on the controlled low-salt diet (Table V).

TABLE IV

PATIENT NO. 1, AGED 27 YEARS, GRAVIDA V, PARA IV. TOXEMIA			
HOURS	HEMATOCRIT	S. PROTEIN	TREATMENT
0	40.2	6.7	Magnesium sulfate 60 c.c.
4	58.1	7.5	(saturated solution)
10	58.1	7.5	hourly, 4 doses. No fluid
16	42.0	7.3	24 hours
24	46.0	7.4	
34	42.0	6.6	
48	42.4	6.5	
72	41.0	6.7	

Drastic reduction in urine volume followed purgation with magnesium sulfate, the highest twenty-four hour output being 790 c.c. and the lowest 225 c.c. The greatest amount of chloride eliminated through the kidney in any twenty-four hour dehydration period was 2.8 Gm. and the lowest was 0.08 Gm.; only two patients excreted more than 2 Gm. The chloride output in the diarrheal stools varied from 0.61 Gm. to 10.8 Gm. but in only two patients was it over 5 Gm. The greatest combined excretion of chloride during a twenty-four hour dehydration period was 10.88 Gm. The total excretion during the longest period of dehydration (four days) was 6.3 Gm. (3.3 Gm. in 1,400 c.c. of urine and 3.0 Gm. in 3,194 c.c. of stool).

TABLE V. WEIGHT, FLUID INTAKE, URINE OUTPUT, AND URINE CHLORIDES ON LOW-SALT DIET

PATIENT NO. 18, AGED 17 YEARS, GRAVIDA I, PARA 0, 33 WEEKS. PRE-ECLAMPSIA					
DAY	WEIGHT (POUNDS)	FLUID		URINE CHLORIDES (GM)	TREATMENT
		INTAKE	URINE		
1	177½				Low-salt
2	173½	2,520	3,100		house
3	171¾	2,340	2,480	5.1	diet
4	171¼	2,420	3,120	2.4	
5	170½	2,160	1,550	1.1	

The urine output in the other group was high, the peak for twenty-four hours being 3,900 c.c. The greatest amount of chloride excreted in the urine during the five-day treatment period after correcting for that from the ingested drug was 6.46 Gm. In five patients an increased urinary chloride excretion was observed during the first three days of ammonium chloride administration but this was followed by chloride retention. In each case the rapid loss of weight occurring during the period of negative balance was followed by weight stabilization as the chloride output was reduced. In the remaining patients chloride was retained and it was noted that if this occurred the total weight loss was less, the maximum being seven pounds and the minimum two pounds as compared with eight pounds and six pounds in those who lost chloride.

General Reactions.—

Those patients rapidly purged were in most instances uncomfortable. They were thirsty, lethargic, and in one instance stuporous, and complained of headache. The constant diarrhea frequently caused marked anal and perineal irritation. The other group was much more comfortable and except for the tasteless food had no specific complaints referable to the therapy.

Discussion

Excessive fluid accumulation outside the vascular system with or without edema may occur in the normally pregnant patient, but it is also an almost constant part of the picture of pre-eclampsia. It is impossible to detect which edematous individual will eventually develop toxemia since in its incipiency the latter condition presents no other diagnostic points except, as Chesley has suggested, an alteration in uric acid clearance which may precede clinical evidence of pre-eclampsia.[8] If the toxemia is allowed to progress to late pre-eclampsia or eclampsia, characteristic physiological alterations, among which are hemoconcentration and oliguria or anuria, develop. We are seeking, by the early recognition and treatment of individuals who are unable to metabolize electrolytes and water normally, to influence the course of pre-eclampsia and if possible to reverse the process at its earliest stage. To accomplish this with the least possible alteration of function is desirable.

The ingestion of a hypertonic solution of magnesium sulfate increases the osmotic pressure within the lumen of the intestine over that of the blood stream and since the salt is only slightly absorbed through the bowel wall fluid is needed to dilute it. The required water is rapidly extracted from the plasma and in an effort to correct the resultant hemoconcentration fluid is withdrawn from the tissues thus decreasing edema. If at the same time the intake of fluid is reduced, a decrease in urine volume follows and automatically limits the amount of sodium chloride which can be eliminated by this route. DeBoer,[9] in a study on dogs, compared the salt and water content of skin and muscle before and after six to seven days without food or fluid. He noted a 4 per cent loss of water from the skin and an increase in the salt content and from the muscle a loss of 1 per cent water and a decrease in salt. After food and fluids were administered the muscle rapidly returned to normal, indicating that isotonic fluid without excess salt had been lost and that no fundamental change had been produced.

The weight loss in the second experimental group was much less spectacular at the onset but the total was pronounced after the mobilization of fluid had begun, and it is noteworthy that when the ammonium chloride ingestion was stopped the weight remained stationary or continued to decrease as long as a low-salt diet was continued. Although in half of this group of patients there was noted an increased chloride output, it is impossible to conclude from this how much loss of sodium and other substances occurred but the failure to accumulate more fluid after the drug was stopped suggests that the tissue electrolytes and therefore the need for water have been reduced and that if the salt intake is maintained at a low level the accumulation of fluid is less likely to recur regardless of how much is ingested. Despite the tissue dehydration, no hemoconcentration was noted because in these patients water is mobilized into a blood stream which has not been depleted of fluid and the blood volume may be increased. Stabilization is then accomplished by an increased urinary output which in turn will permit a greater excretion of solids. The major effect of ammonium chloride in the mobilization of body chlorides and fluid was noted

during the first three days of its use. This is to be expected because breakdown of the drug and its conversion to urea in the liver allowing for an increased electrolyte output ceases at about this time and is re-established only after a few days' rest. If ammonium chloride is expected to obtain a maximum effect it must be given intermittently and not continuously.

In the management of the patient with early pre-eclampsia the aim in treatment is to reverse the abnormal flow of fluid and to eliminate the excess interstitial water. That this can be accomplished by a regimen which is more acceptable to the patient than fluid limitation and purgation and which produces no deleterious physiological alterations is demonstrated by this study. A controlled salt-poor diet alone without fluid limitation resulted in a 2 to 7 per cent loss of total body weight in from two to four days. Since these patients had all been instructed on a similar regimen as outpatients without response it seems likely that the failure was not due to the type of therapy but to failure to adhere to the prescribed diet. This became evident in several who rapidly regained their lost weight after discharge from the hospital and who were subsequently readmitted and easily controlled by limitation of salt alone. Thus it appears that for most patients with fluid retention associated with normal pregnancy or with pre-eclampsia neither limitation of fluid and purgation nor ammonium chloride is necessary if the salt intake is reduced.

We have not found it necessary to restrict the fluid intake during pregnancy even in the edematous patient; rather, we encourage her to take fluids and reduce salt. That an adequate intake is important is demonstrated by a study of Chesley and Annitto[10] of 237 clinically normal patients who presented excess fluid retention in late pregnancy. They found that those treated by restriction of both salt and water had a higher incidence of subsequent toxemia than those on a reduced salt and increased fluid regimen. An extremely low salt diet is not well tolerated over prolonged periods of time but as indicated in this study undue restrictions usually are unnecessary since a rapid weight loss follows the use of a diet containing about 2 Gm. of salt daily. Nontoxic prenatal patients in whom abnormal water retention is suspected are given a trial on such a diet as outpatients; if after reinstruction and encouragement weight and edema continue to increase they are admitted to the hospital. The initial inpatient therapy consists solely of the same diet with adequate fluids; in some cases ammonium chloride is administered later. Hospitalization of such patients is important not only to accomplish dehydration but because they learn exactly what is meant by a low-salt diet. After discharge all such patients are followed for the remainder of their prenatal periods in our toxemia clinic. Frequently those who had failed to lose weight prior to hospitalization are able to carry out our instructions without difficulty at home but others require repeat hospitalization either for control of edema or because of the appearance of signs of toxemia.

For severe pre-eclampsia and eclampsia neither of these methods is adequate. Classical dehydration exaggerates the pathological changes characteristic of severe toxemia (hemoconcentration and oliguria) and may even result in peripheral circulatory collapse. The reduction in blood flow through both the general circulation and the kidneys increases anoxemia and reduces urine output

and is diametrically opposed to what we consider to be rational treatment. Diet and ammonium chloride do not produce their dehydrating effect rapidly enough in such a crisis and forcing fluids may simply increase edema; in this late stage of toxemia it is difficult to produce a water diuresis because the loss of fluid from plasma to the tissues is abnormally exaggerated and the more that is ingested the greater becomes the edema. The rapid mobilization of fluid which is required can be obtained only by the injection of hypertonic glucose solutions or concentrated plasma, both of which will dehydrate the tissues and dilute the blood, thus aiding in the control of convulsions, increasing oxygenation, and providing sufficient fluid for the formation of urine.

Conclusions

This study of two methods of reducing excess fluid accumulation in the tissues during normal and toxemic pregnancy indicates that purgation and limitation of fluid intake is unnecessary for dehydration. If the salt intake is sufficiently reduced the tissue fluid is mobilized into the blood stream and excreted by the kidneys without decreasing the blood volume. The addition of ammonium chloride to a low-salt diet increases chloride output for a period of about three days during which time a rapid weight loss may be noted. This is followed by a period of chloride retention and weight stabilization. Neither classical dehydration nor simple salt reduction is adequate for the treatment of severe pre-eclampsia and eclampsia since the former exaggerates the pathological changes characteristic of these conditions and the latter does not produce its effect rapidly enough.

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Discussion

DR. S. A. COSGROVE, Jersey City, N. J.—The treatment of certain phases of biochemistry involved is interesting and thought stimulating, but time permits discussion only of its clinical conclusions.

The authors state that a change to positive water balance is a normal accompaniment of pregnancy, and consider that this shift "may be exaggerated to a point at which edema . . . appears." They thus accept some degree of both occult and actually demonstrable edema as normal phenomena in many cases of pregnancy.

Later they state, "the earliest clinical sign of developing pre-eclampsia is an increased retention of water which may be evidenced only by an abnormal increase of weight," and "fluid retention is an early sign of pre-eclampsia and . . . its treatment is important," advising that at this stage intensive therapy be directed toward reversing the flow of fluid.

Without quarrel with the actual validity of both these statements, which would superficially seem to be at some variance, I do not think it helpful as the basis of management of toxemic pregnancies, to concede at all the occurrence of "physiological edema of pregnancy," for this opens wide the gate to a careless tolerance of excessive degrees of edema by a large number of practitioners as "physiological," not worth intensive therapy directed against it. It would appear to me safer to insist that *any* degree of edema, even that manifested only by excessive weight gain, is essentially abnormal, unphysiological, dangerous, necessitating alert attention and active therapy.

The authors present a study wherein they seek to establish a valid basis of management to reverse the shift of water balance. It might be a little more impressive if it embraced a larger series, for more cases would have made less glaring the rather extreme ranges of some of their figures.

Nevertheless, their results do most usefully show that treatment by active purgation and extreme liquid restriction, while of course successful in reducing weight and edema, is so only at the expense of great subjective discomfort and the causation of a number of distinctly pathological effects, sometimes to the point of actual danger.

On the other hand, treatment by simple bed rest and salt restriction produces these desiderata entirely within the range of physiology, at the expense only of the subject's patience, and negligible subjective unpleasantness. They point out the ephemeral value only of ammonium chloride as adjuvant to this simple regime, and the necessity of expediting it by the parenteral use of hypertonic glucose.

For many years our own therapeusis, based on the observation of clinical results, has accorded almost exactly with the principles here worked out. We appreciate their substantiation of the basis of our own practice.

DR. FRANK E. WHITACRE, Memphis, Tenn.—Living and working in the "eclamptic belt" has made me very interested in the problems brought forth this morning. It was my privilege several years ago to study two groups of 100 consecutive cases each. One series was on our service in North China, and the other in Memphis, Tenn. We brought out at that time that on opposite sides of the world—the one in a cold, dry climate and the other in a moist, warm one—there was very little difference in the blood chemistry and physical findings and that color and race had very little to do with the problem. Study of the Chinese, the Negroes, the white Americans, and the mixture of races brought out that they had only one thing in common, and that was that the disease was seen more frequently in the underprivileged group. I examined the birth records in the private hospitals in the city of Memphis and found that eclampsia, although common in the charity hospital, was rare in the private hospitals. Of the cases occurring in the private hospitals, most of these patients had been admitted on the charity service. It seems probable that toxemia of late pregnancy at least is related to nutritional deficiencies.

DR. WILLSON (Closing).—To answer Dr. Cosgrove, we are very loathe even to suggest that the patient who retains excessive fluid is normal despite the fact that she may complete her pregnancy without any evidence of pre-eclampsia. Each patient who gains abnormally, with or without edema, is referred immediately to the toxemia clinic and she is followed throughout the pregnancy in that clinic, even though she develops no other signs of toxemia.

HYPERPLASIA OF THE ENDOMETRIUM, ITS RELATIONSHIP TO HYPERTROPHY AND HYPERPLASIA OF THE UTERINE VESSELS*

OTTO H. SCHWARZ, M.D., AND ALFRED SHERMAN, A.B., M.D., ST. LOUIS, MO.

(From the Department of Obstetrics and Gynecology, Washington University School of Medicine)

IN REVIEWING a series of sections from the uterus, including the entire thickness of endometrium and peritoneum, in search of early development of myomas from uterine blood vessels, it was noted in passing that whenever we encountered a marked case of hyperplasia of the endometrium, there was an accompanying hypertrophy and hyperplasia of the uterine arteries, especially marked in the lower middle third of the uterine wall.

The sections showing hyperplasia were set aside as they were encountered for the purpose of study in detail of this interesting relationship. In the description of hyperplasia of the endometrium in the standard textbooks, the pathological descriptions refer in most instances only to the endometrium itself, particularly the character of the glands and stroma. No special remarks are made concerning the hypertrophic condition of the uterine wall and no definite references to the hypertrophy and hyperplasia of the vessels. Some 200 specimens were set aside in which the hyperplasia of the endometrium was quite striking to very marked. In general, every one of these specimens shows definite hypertrophy and hyperplasia of the vessels of the lower middle third as well as the inner third. In order to evaluate these changes we studied a series of uteri which were not excessively enlarged and which also had no accompanying hyperplasia of the endometrium. Our findings here were that the picture of the uterine circulation as a whole is somewhat variable. In some instances we could determine what we call a normal pattern, i.e., the vessels of the lower endometrium were very small, the vessels of the inner third moderate in size with comparatively few nuclei in the media of the wall, and in the lower middle third usually no activity was seen. Occasionally we would see a definite tendency for these lower vessels to be stimulated to some degree but in no instance as markedly as in the average case of hyperplasia.

We immediately concluded that in studying the character of these vessels the question of the parity of the individual had to be considered because we were well aware of the fact that in parous uteri, which show evidence of marked chronic subinvolution in the circulatory system, they are different in character from those in a nulliparous uterus. It was found that, whether the vessels were in nulliparous, primiparous, or multiparous individuals, the abnormal stimula-

*Presented at the Sixtieth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 8 to 10, 1949.

Fig. 1

Fig. 2

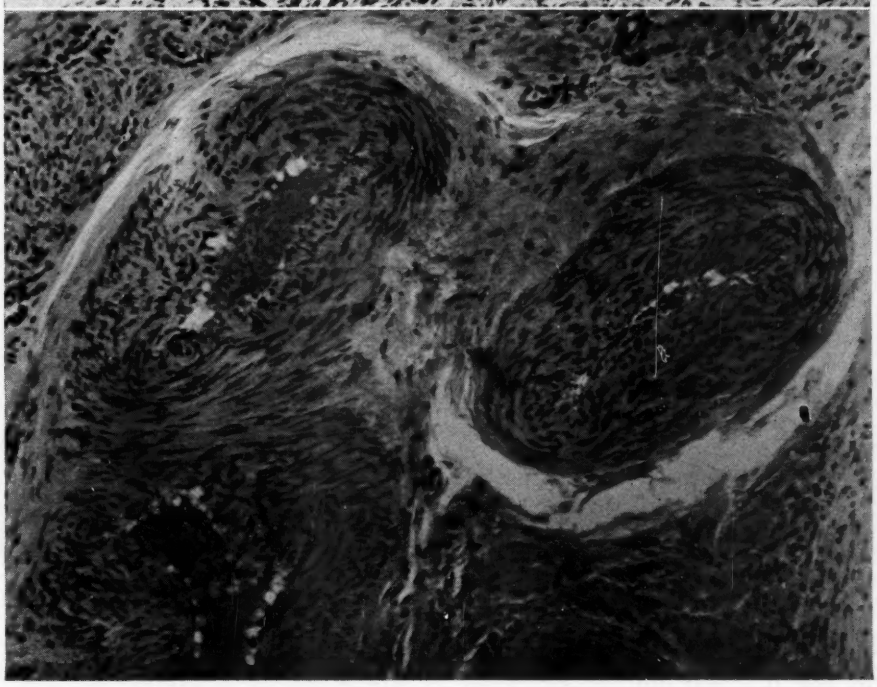

Fig. 3

Fig. 1.—Marked hyperplasia of endometrium (Swiss-cheese pattern). Hypertrophy of uterine wall. Hypertrophy and hyperplasia of blood vessels, especially outer two-fifths.

Fig. 2.—Blood vessels of inner third of uterus. Hypertrophy and hyperplasia, with thickened media and increased cell content.

Fig. 3.—Lower middle third of uterus. Higher power of Fig. 1. Hypertrophy and hyperplasia of arteries.

tion which we think is due to estrogen and progesterone in combination produces the same picture, regardless of the original condition of the vessels.

In discussing these findings with Novak of Baltimore, he suggested studying the condition of the vessels from the endometrium in these cases. In other words, to see whether this hypertrophy and hyperplasia are present there as well. This was done, and we can emphatically state that it is in many instances quite conspicuous but by no means in all.

Fig. 4.—Marked hyperplasia of endometrium (glandular pattern). Hypertrophy of uterus. Hypertrophy and hyperplasia of blood vessels, especially of the middle third.

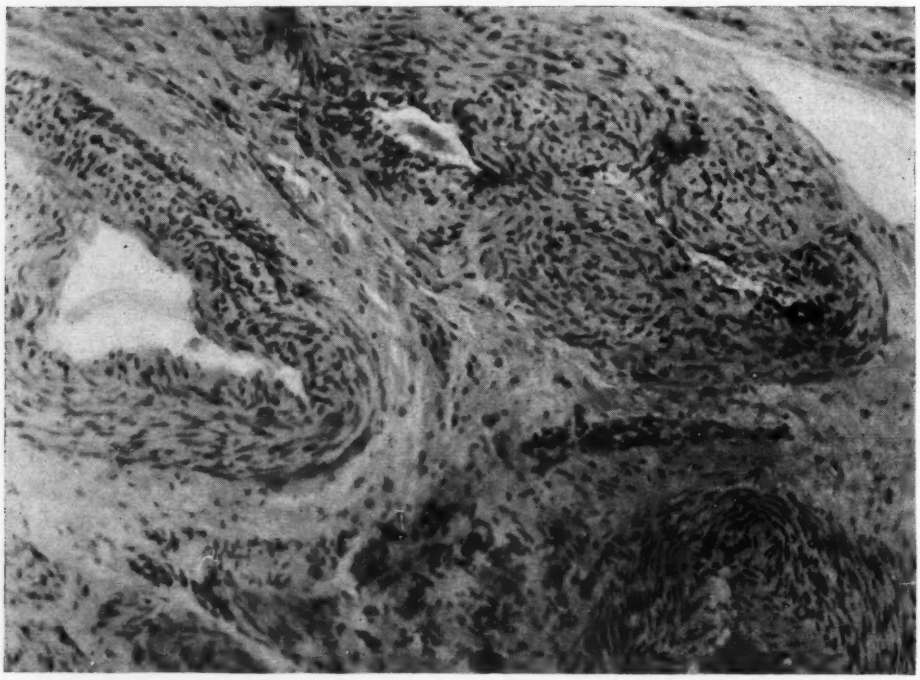

Fig. 5.—Middle third of uterus. Higher power of Fig. 4. Hypertrophy and hyperplasia of blood vessels.

In order to bring out the points of similarity of the lesions of the vessels in various types of uteri, we are including a tabulation (Tables I, II, and III) of 50 specimens divided between nulliparous, primiparous, and multiparous speci-

TABLE I. HYPERTROPHY AND HYPERPLASIA OF UTERINE VESSELS IN CASES OF HYPERPLASIA OF THE ENDOMETRIUM

NULLIPAROUS UTERI

CASES	VESSELS		
	ENDOMETRIUM	INNER THIRD OF UTERUS	LOWER MIDDLE THIRD OF UTERUS
1	1	2	3
2	1	2	3
3	3	3	3
4	3	3	3
5	3	2	3
6	3	3	3
7	2	3	3
8	2	3	3
9	1	3	3
10	3	3	3
11	2	3	3
12	1	3	3
13	2	3	3
14	2	3	3
15	3	3	3

Key to Chart:
1, Definite hyperplasia and hypertrophy.
2, Marked hyperplasia and hypertrophy.
3, Very marked hyperplasia and hypertrophy.

TABLE II. HYPERTROPHY AND HYPERPLASIA OF UTERINE VESSELS IN CASES OF HYPERPLASIA OF THE ENDOMETRIUM

PRIMIPAROUS UTERI

CASES	VESSELS		
	ENDOMETRIUM	INNER THIRD OF UTERUS	LOWER MIDDLE THIRD OF UTERUS
16	1	3	3
17	0	2	3
18	2	3	3
19	0	3	3
20	0	3	3
21	2	3	3
22	0	2	3
23	0	1	3
24	0	2	2
25	2	3	2
26	2	3	3
27	1	2	2
28	3	3	3
29	1	3	3

Key to Chart:
1, Definite hyperplasia and hypertrophy.
2, Marked hyperplasia and hypertrophy.
3, Very marked hyperplasia and hypertrophy.

mens. In these tables, it is interesting to note that the vessels of the lower middle third all showed excessive hypertrophy and hyperplasia, and with few exceptions the whole uterus was enlarged. It made no difference whether there were no myomas in the uterus, or there was chronic subinvolution. The arteries of the inner third were markedly hypertrophic and hyperplastic with few exceptions and, in the remainder, the changes were still definitely striking. In considering the condition of the vessels of the endometrium itself, it was supposed that, if these vessels were enlarged, it might be due to a residual condition of repeated pregnancies, but in the cases reviewed this is clearly not the case. The

most striking increase in thickness of the vessel walls of the endometrium was in the nulliparous individuals. We consider the vessels increased in size and thickness if they show a definite media of muscle tissue. In a perfectly normal endometrium, one occasionally sees vessels of this type, but we have never seen them strikingly in the absence of hyperplasia. Another interesting observation concerned uterine polyps in situ. There is hyperplasia of the vessels in such polyps. The vessels showed the most striking increase in caliber and thickness. This condition of increased size of the endometrial vessels is most striking in the lower half but occasionally we will see it even quite near the surface as is shown in Figs. 6 and 7.

TABLE III. HYPERTROPHY AND HYPERPLASIA OF UTERINE VESSELS IN CASES OF HYPERPLASIA OF THE ENDOMETRIUM

MULTIPAROUS UTERI

CASES	ENDOMETRIUM	VESSELS	
		INNER THIRD OF UTERUS	LOWER MIDDLE THIRD OF UTERUS
30	0	3	3
31	2	3	3
32	3	3	3
33	0	3	3
34	2	2	3
35	1	3	3
36	1	3	3
37	1	2	3
38	0	2	3
39	1	2	3
40	2	2	3
41	0	2	3
42	2	3	2
43	2	3	3
44	1	3	3
45	2	2	3
46	2	3	3
47	2	2	2
48	2	3	3
49	2	3	3
50	3	3	3

Key to Chart:

1, Definite hyperplasia and hypertrophy.
2, Marked hyperplasia and hypertrophy.
3, Very marked hyperplasia and hypertrophy.

In order to bring out these vessel changes more strikingly, we have included illustrations in which we consider first the normal nulliparous artery of the middle third, showing its nuclear content and tissue in the wall (Fig. 8); also a multiparous uterus which shows the changes of subinvolution strikingly in the hematoxylin-eosin stain and also brings out with the orcein van Gieson stain a marked amount of dead elastic tissue and other material in its wall. In this section it is to be noted that there are comparatively few nuclei in the media of the vessels. At the same time, this type of vessel can be stimulated, producing hypertrophy and hyperplasia of the wall. In hyperplasia of the endometrium, these vessels similarly become hyperplastic just as in the case of the nulliparous vessels (Fig. 9).

Third, in observing these vessels in our study, it occurred to us that, during pregnancy when the vessels become very hypertrophic, a hyperplastic development might also be present. This was found to be true. We went over some 45

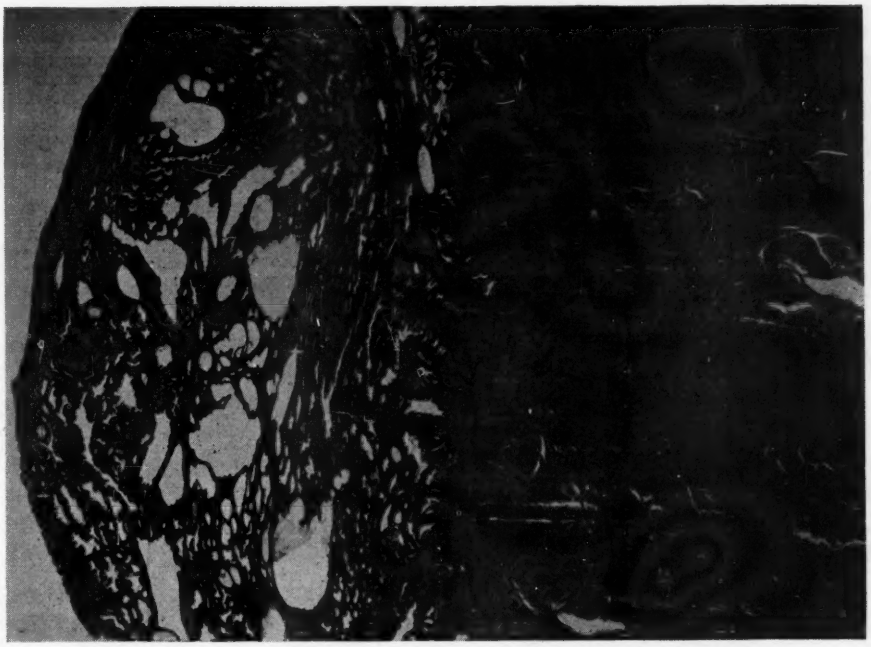

Fig. 6.—Marked hyperplasia of the endometrium (Swiss-cheese pattern). Hypertrophy and hyperplasia of blood vessels of the endometrium. One group of vessels can be seen in midline of picture near endometrial surface. Another group present in upper right portion of the endometrium, but well within endometrial area.

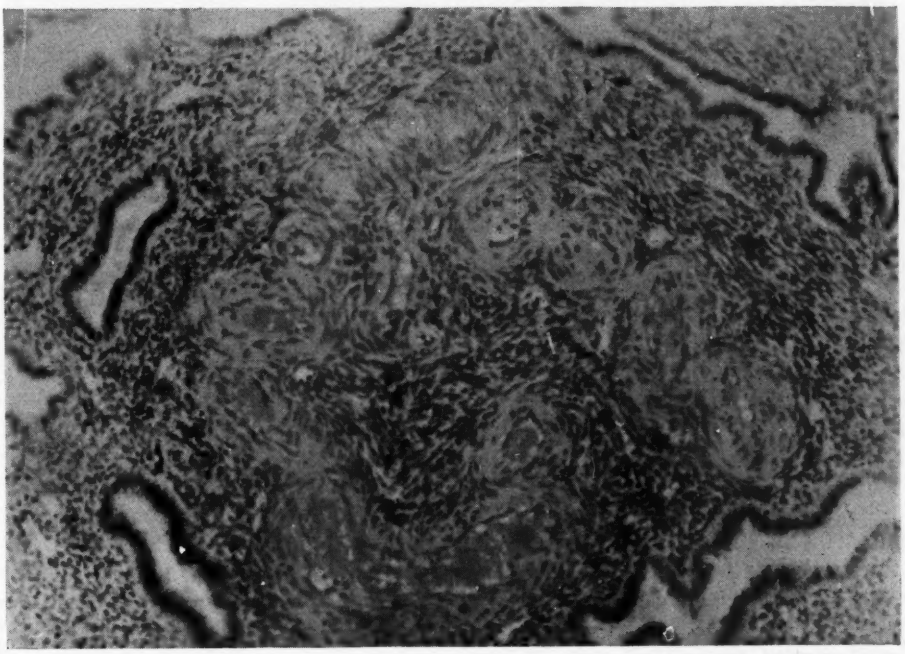

Fig. 7.—Higher power of Fig. 6. Upper group of arteries near endometrial surface. Note the increase in caliber; also the well-developed media of these vessels.

Fig. 8.

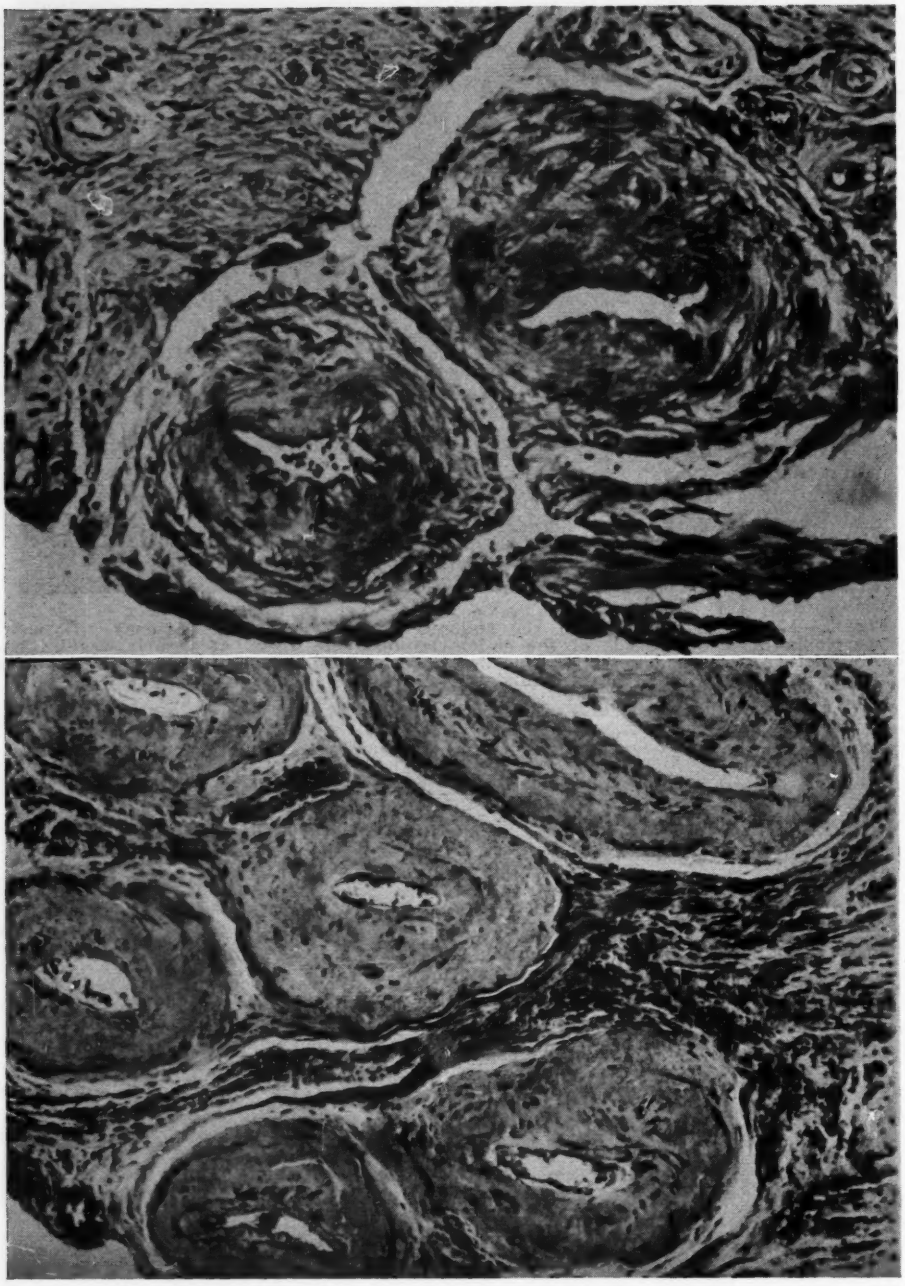

Fig. 9.

Fig. 8.—Middle third of uterus, normal arteries, nulliparous. Compare with Figs. 3 and 5.

Fig. 9.—Middle third of uterus. Multiparous uterus, vessels in state of marked chronic subinvolution. Hematoxylin and eosin. Hyaline-appearing wall due to diffused dead material, lack of absorption during involution. Mixture of elastic and muscle tissue, but stains homogeneously as elastic tissue. Note the evenly scattered nuclei throughout the media. Vessels of this character can become hyperplastic as well as those from a nulliparous uterus.

sections of uteri showing the placenta and the peritoneum in various months of pregnancy and the findings were most remarkable and interesting. We are reporting these changes during various months of pregnancy in a subsequent study which will be presented in the near future. Here, however, as a matter of comparison, we will show an illustration (Fig. 10) which shows how rapid and marked these changes are in pregnancy. The section in this case is from a uterus of a woman who was 12 weeks pregnant. It was her first pregnancy and was terminated by one of the staff surgeons because of decompensated heart disease.

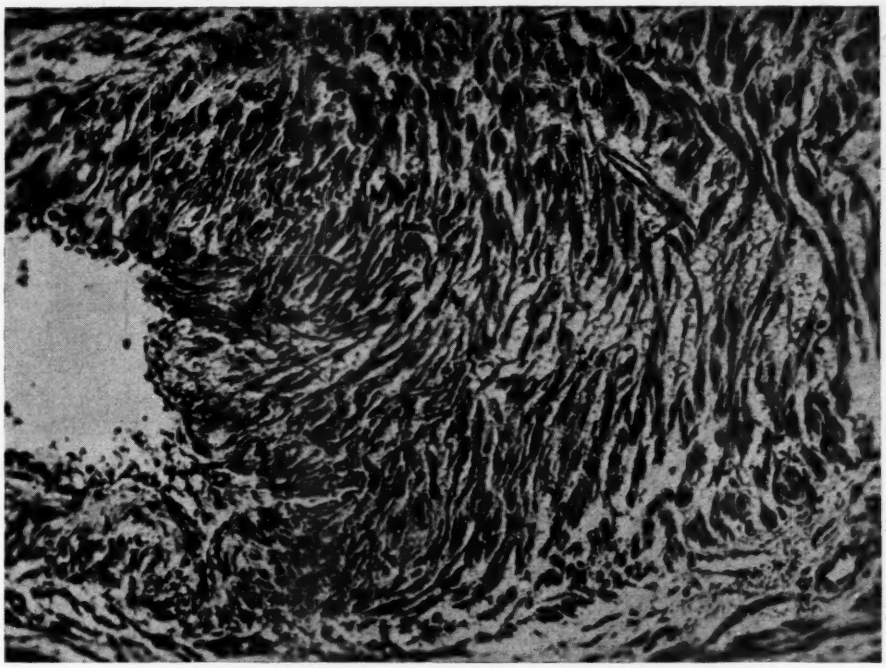

Fig. 10.—Pregnancy 12 weeks, primiparous. Artery, middle third of uterus, about one-third of vessel showing. Note the large size of the muscle cells of the media with striking hyperplasia and running off into the adjacent tissue. Compare with normal vessels in Fig. 8. This marked change has taken place in a period of 12 weeks.

In studying this picture, it must be remembered that these vessels were simple nonhypertrophic vessels of a nulliparous individual 13 weeks before. In a period of 12 weeks these very striking changes have taken place. They are very marked in both arteries and veins and more particularly in the veins. The condition at 12 weeks, as the picture shows, is very striking. The proliferation of the cells of the media of the vessels, both veins and arteries, is tremendous. They look very much like muscle cells of a more advanced pregnant uterine musculature. The cells are running away into the uterine wall in all directions, indicating that the hyperplasia of the muscle cells in the uterus during pregnancy, as Stieve has stated, must come from this source and not from any other condition. He did not emphasize vessel origin but stated that new muscle cells arose from histiocytes in adventitial connective tissue. This will all be reported subsesquently in detail. This condition at 12 weeks is most interesting to us because it is at this time in pregnancy that the estrogen level is quite high and the corpus luteum is at the height of its development, indicating that this normal change is due to a combined stimulation of estrogen and progesterone.

Knowing full well that hyperplasia of the endometrium has been obtained by many observers by stimulation with estrogen, we thought that by some experi-

ments with virgin rabbits we might be able to reproduce the picture which we have just described for the human being. This we were able to do with very little difficulty. In order to produce excessive growths, we injected rabbits for 12 weeks, 3 mg. of stilbestrol 3 times weekly. One received 3 mg. stilbestrol twice weekly for 3 weeks, and then, in addition, 1 mg. of progesterone 3 times weekly until autopsy at 12 weeks.

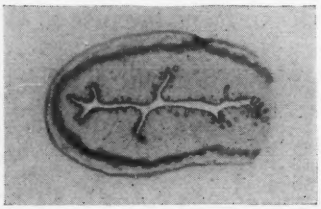

Fig. 11.—Section of uterus of rabbit 5 to 6 months old, virgin. Fig. 12 and Fig. 14 taken at the same magnification for comparison. Uterus comparatively small, dark middle strand is well-developed smooth muscle. Note no conspicuous blood vessels.

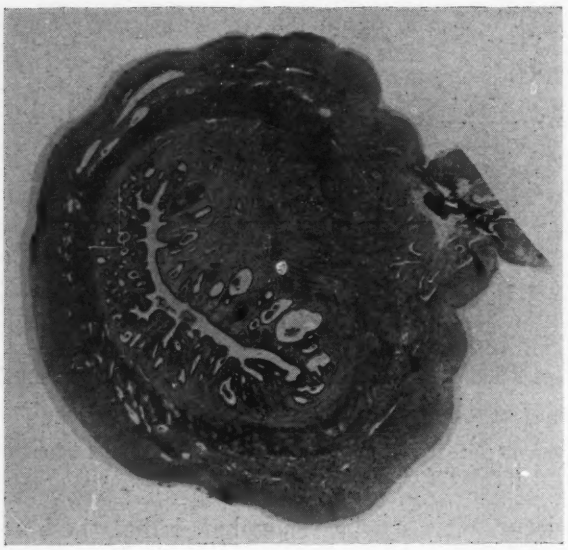

Fig. 12.—Virgin rabbit uterus, stimulated by estrogen (for dosage see text). Period 3 weeks. Same age as rabbit of Fig. 11. Note well-developed "Swiss-cheese" hyperplasia, increased musculature, and some hypertrophy and hyperplasia of vascular system.

In studying sections of these uteri it is obvious that overdosing caused first hyperplasia, then necrosis of the endometrium. The hyperplasia of the endometrium which must have been present at a much earlier period has disappeared. The endometrium is necrotic and all the glandular elements are practically destroyed. There is also a necrosis of the inner portion of the muscle layer, but, interestingly enough, in both specimens the vascular tree is still in a state of marked hypertrophy and hyperplasia. We then considered that by treating animals similarly for a period of 3 weeks we should catch the picture of marked hyperplasia with the accompanying vessel changes, and this we did.

Figs. 12 and 13 show the condition of the animals treated with estrogen for 3 weeks. This shows a striking Swiss-cheese pattern and a hypertrophy of the musculature, and some hyperplasia and hypertrophy of all the vessels. The specimen in which progesterone was added shows all these changes even more

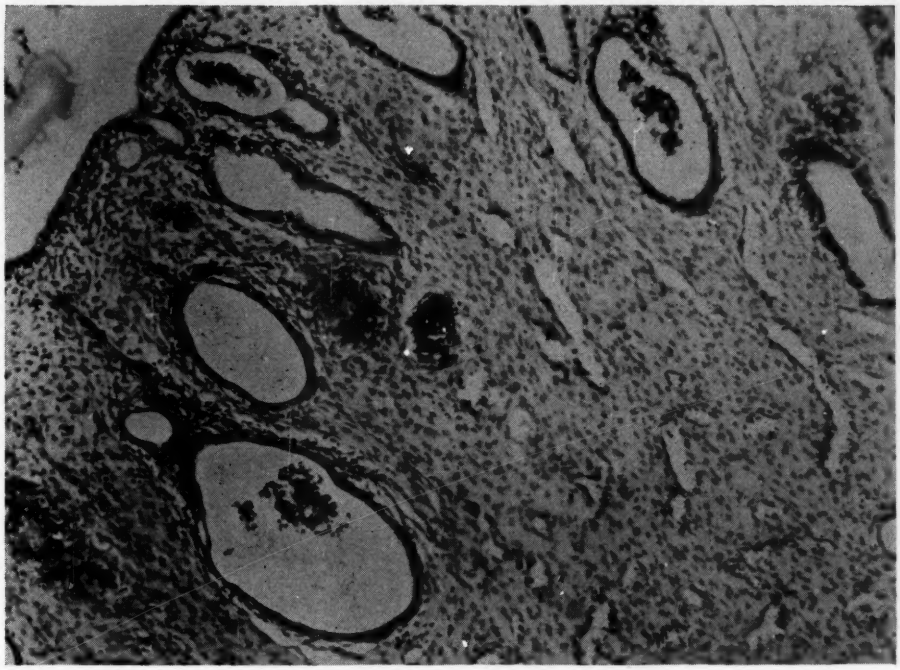

Fig. 13.—Endometrium of Fig. 12 showing hyperplasia very strikingly. Vessels showed only moderate hyperplasia.

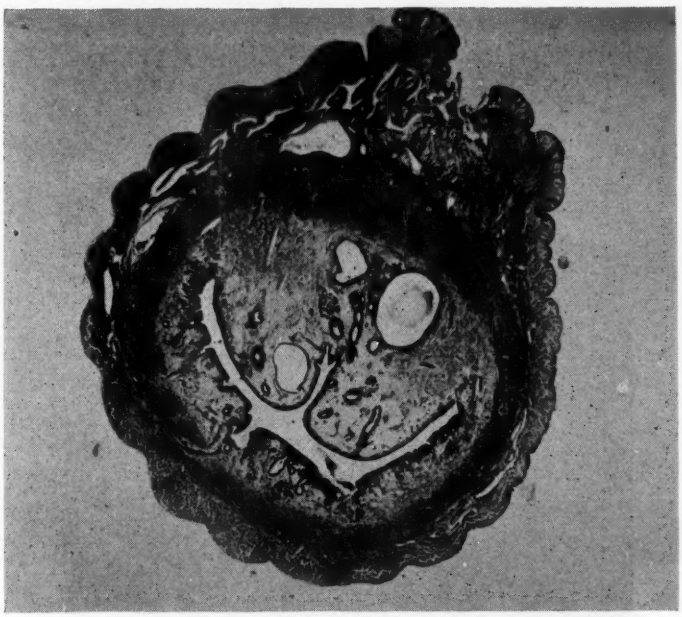

Fig. 14.—Virgin rabbit uterus, stimulated with estrogen and progesterone (for dosage see text). Period 3 weeks. Same age as rabbit of Fig. 11. Over-all picture shows endometrium, uterine wall, and vascular system much more strikingly. Note especially markedly hypertrophic vessels in upper right portion of the picture.

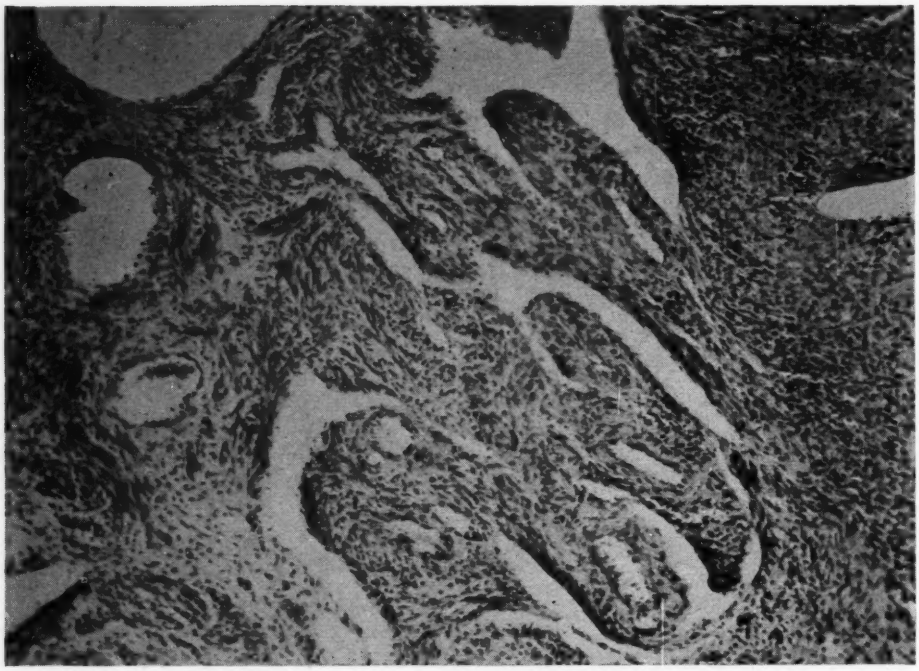

Fig. 15.—Outer half of uterine wall of Fig. 14 showing very marked hypertrophy and hyperplasia of the uterine blood vessels.

Fig. 16.—Uterus of monkey, marked hyperplasia of endometrium, estrogen stimulation, previously reported by R. J. Crossen, St. Louis, Mo.

Fig. 17.

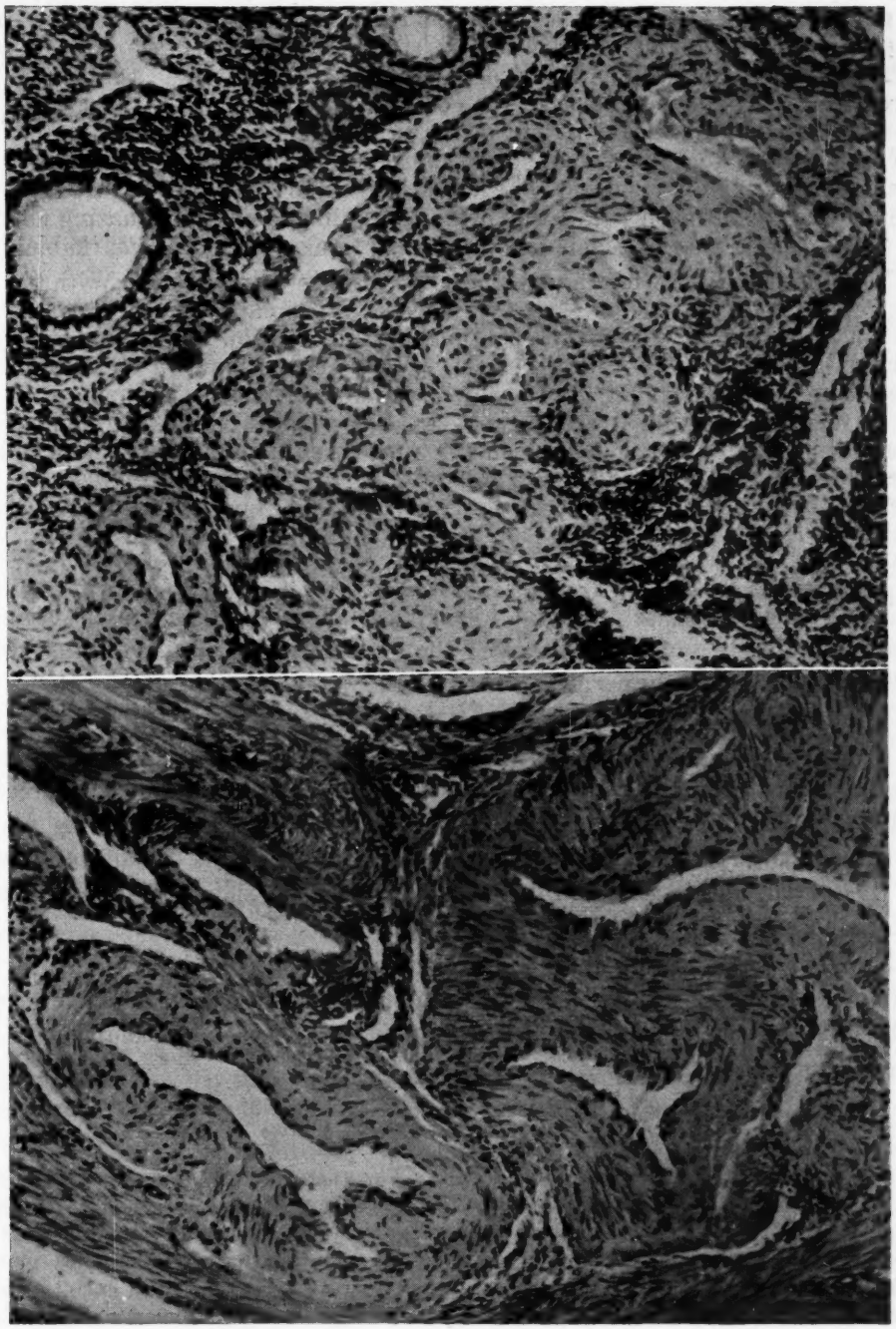

Fig. 18.

Fig. 17.—Monkey. Marked hyperplasia of the arteries of the upper endometrium. Compare with Fig. 7 in the human being.

Fig. 18.—Monkey, same as Fig. 16, middle of hypertrophied uterine wall, showing marked hypertrophy and hyperplasia of blood vessels.

strikingly. The Swiss-cheese pattern is exaggerated, the uterine wall is more hypertrophied, and the vessels are considerably thicker even than when estrogen was given alone (Figs. 14 and 15). In other words, we produced in these rabbits a picture entirely analogous to what we see in the uterus in chronic cases of hyperplasia of the endometrium. The striking picture of these cases can be best appreciated by comparing them to the control rabbit in Fig. 11, the control picture taken at the same scale as that of the injected animals, and the comparison is of course strikingly obvious. Very meager endometrium is present. The muscle wall is of very moderate thickness in comparison and the circulation is difficult to make out even with low-powered magnification. The amazing changes that took place in these animals in three weeks to us were most remarkable.

We were familiar with the work of Dr. Crossen in monkeys. With the use of estrogen alone he produced a very marked hyperplasia of the endometrium even to the extent of polypoid formation, but no mention in his study is made of the enlargement of the blood vessels. We were fortunate in obtaining from Crossen one of the paraffin blocks which we had sectioned. This specimen not only showed the striking hyperplasia but the very large vessels throughout the endometrium containing a definite media with large amounts of smooth muscle (Figs. 16, 17, and 18). The uterine wall, itself, was hypertrophied and the vessels of the uterine walls were likewise markedly hypertrophied and hyperplastic.

Comment

From this study we feel that hyperplasia of the uterine vessels is an accompanying feature of hyperplasia of the endometrium. It is strikingly seen in all cases of marked hyperplasia, even to the extent of hyperplasia of the vessels of the inner third and of the endometrium itself.

From reviewing many cases we feel that the stimulus that brings this all about first acts upon the vessels of the lower middle third, gradually increasing the blood supply of the inner third, and thereby bringing stimulating factors into the endometrium in larger amounts. If the condition is of sufficient standing, then even the vessels of the lower endometrium show these hyperplastic conditions very strikingly themselves.

Finally, with the abnormal stimulation of estrogen and progesterone, the uterine vessels show even a more striking picture of hyperplasia and hypertrophy than the endometrium in hyperplasia, and the usual accompanying hypertrophy of the uterine wall.

440 North Newstead Avenue.

Discussion

DR. FREDERICK H. FALLS, Chicago, Ill.—Drs. Schwarz and Sherman have demonstrated clearly that the stimulus which results in the hypertrophy and hyperplasia of the endometrium acts also on the blood vessels of the uterine wall in a similar manner. Physiologically it could hardly be otherwise since increased circulation is essential to all forms of overgrowth. However, it seems to me that the degree of hypertrophy as shown in Dr. Schwarz' slides is unexpected and unusual, and we are indebted to him.

The changes noted in the blood vessels must be secondary to increased anabolic activity brought about by the same stimulus that produced the changes in the endometrium and myometrium. This presupposes an increase in the oxygen supply to these cells since intracellular anabolic ferments cannot otherwise become activated to the degree necessary to produce hypertrophy. Hormonal stimulation, possibly estrogen and progesterone as

suggested by the authors, or possibly the growth hormone from the hypophysis, may be the responsible factor.

The same mechanism is at work when the muscle cells of the uterine wall and blood vessels hypertrophy during pregnancy. In these cases there is the additional factor of work hypertrophy caused by the increased intrauterine tension and motility resulting from the development of the fetus and placenta.

In the nulliparous and nonpregnant uteri studied by the essayists no such factor is apparent. One might suggest that study of the motility and irritability of the uterus in these cases with an intrauterine balloon might throw some light on the cause of the changes here described.

The clinical implications of these observations are interesting. With the formation of a hyperplastic endometrium it is only one step further to the formation of polyps either single or multiple. These being well supplied with blood by the hyperplastic blood vessels, bleed freely themselves and this blood loss may be supplemented by bleeding from the hypertrophied endometrium to a degree that sometimes approaches exsanguination. It is obvious that removal of the polyp or hyperplastic endometrium is of temporary value only and that the underlying stimulus must be reduced to effect a cure.

Likewise, excessive hemorrhage in incomplete abortion can be well explained by the hyperplasia in these vessels. Removal of the placental remains is not sufficient to control bleeding in many cases but must be combined with strong oxytocics to compress these hypertrophic vessels.

There are two points in their experimental work which need comment. First, as they have noted, the doses of estrogen and progestin per pound of rabbit weight were enormous and produced a lesion quite different from that seen in the human material studied. Changes produced in uteri of women who were about to be hysterectomized after the injection of suitable doses would be more convincing. Furthermore, it is dangerous to assume that changes produced by various stimuli in animal tissues can be assumed to occur in the human being after similar injections.

I wish to call the attention of this society to the feasibility of noting increase in the size of uterine arteries on vaginal examination when the uterus is enlarged because of pregnancy or fibromyomas. These are similar to the changes described by the writers but are extrauterine. In a rather large percentage of cases this hypertrophy can be felt in the vaginal fornix on one or both sides. The position of the artery varies with the degree of rotation of the uterus and the number and position of the fibroids in the lower part of the uterus. We have used this enlargement of the vessels to help diagnose an enlarged uterus when, because of obesity or rigidity of the abdominal wall the outline of the uterus could not be made out. Also, in a given case of a pelvic tumor that cannot be outlined for the same reasons, if hypertrophied uterine arteries can be palpated the tumor is probably uterine. If they cannot be made out, or are seemingly small, an ovarian or paraovarian origin of the tumor is more likely.

DR. RALPH E. CAMPBELL, Madison, Wis.—In this investigation, several uterine specimens were studied in which there was no endometrial hyperplasia and the uteri were reasonably normal as to size. This was done to establish a normal vascular pattern. In the specimens with no endometrial hypertrophy the vessels of the lower middle third as well as the middle third were reasonably normal as to vascular pattern. However, in a comparative series of uteri with endometrial hyperplasia all specimens invariably showed hypertrophy and hyperplasia of the vessels in the lower middle third and inner third of the uterus. These findings in themselves seem conclusive, that whether or not the vessels in the uterine wall show these changes is dependent upon endometrial hyperplasia.

Proceeding from the above observations, the investigators decided to study the circulatory changes in the endometrium itself.

I have studied the microphotographs which have been presented in great detail and they are conclusive.

The experimental evidence as shown in the rabbits and monkey reinforces the histopathologic findings in the human being.

Indeed the microphotographic illustrations as shown in the monkey certainly present a clear picture to support the conclusions in this investigation.

It is of interest to note that in virgin rabbits, 5 to 6 months old, the changes are more marked in the endometrial hyperplasia with estrogen and progesterone than in estrogen alone. In addition, the virgin rabbit exposed to excessive estrogen dosage showed a marked endometrial and myometrial necrosis, with the vascular system prominent but retrogressing.

Necrobiosis, leucocytic infiltration, and thrombosis are commonly seen in endometrial hyperplasia and functional bleeding in the human being.

I am sure that most of us who have been interested in endometrial patterns have noted hyperplasia and hypertrophy of the vessels in endometrial hyperplasia and have passed off these findings simply as an interesting observation. In talking to our pathologist at the University Hospital, I discussed with him the findings of the authors relative to endometrial hyperplasia. His comment was, and I quote, "I have noted these findings in the blood vessels in glandular hyperplasia and have wondered what importance should be placed upon them."

I am wondering whether it was noted that the changes of hypertrophy and hyperplasia of the arteries were primarily in the coiled arteries supplying the superficial and middle third of the endometrium or in the short straight arteries supplying the basal third of the endometrium?

Markee describes the contraction cones at the base of the coiled arteries and their importance in the bleeding process. This fact has also been emphasized by Bartelmez and others. Do the hypertrophy and hyperplasia begin in that area? And, if so, is it any greater in that area?

It would seem to me that, with the rise and fall in hormonal levels with fluctuation in endometrial growth and regression, there would be a greater disproportion in the coiled arteries under such conditions of hypertrophy and hyperplasia as discussed in this thesis, thereby resulting in ischemia, stasis, necrosis, and finally abnormal bleeding. Certainly the bleeding mechanism is of greatest importance and of practical significance.

It would be of interest for the authors to extend their research to those conditions in the human being accompanied by hyperestrinism and abnormal bleeding, namely, abnormal functional bleeding, feminizing tumors, and pregnancy with early interruption.

This presentation is commendable and the results of this investigation may lead to still more important observations.

DR. ROBERT L. FAULKNER, Cleveland, Ohio.—It is my belief that there is in the physiology of these vessels that Dr. Schwarz had so admirably pointed out a great deal more than meets the eye.

The solution of the problem of uterine bleeding will probably be by physiologic, rather than morphologic, methods; but those of us who see the tragedies of uterine bleeding day after day must do what we can in at least crystallizing our own ideas.

DR. EMIL NOVAK, Baltimore, Md.—During the past two years Dr. Schwarz has been engaged in a number of fundamental histologic studies, and his presentation today, dealing as it does with the vascular changes in hyperplasia, is a valuable contribution. The epithelial, glandular, and stromal characteristics of hyperplasia throw no more light on the mechanism of the abnormal bleeding than the corresponding histological changes of the normal cycle do on the mechanism of normal menstrual bleeding. After all, menstruation is a vascular phenomenon, and it is to the blood-vessel apparatus that we must go for an explanation, important as the hormones are as motivating factors.

Schroeder, it will be recalled, has always held that the source of the bleeding in hyperplasia is in the small areas of necrobiosis found with this lesion, which undoubtedly occur, though in my own experience they have often been few in number and rather minute. It is difficult for me to believe that such small areas can be the source of the

massive hemorrhage sometimes seen in association with hyperplasia, especially as the far more extensive loss of tissue seen in the normal cycle is attended with shorter and more moderate bleeding, at times even scanty. Some other factors must be concerned, probably a factor increasing the permeability and fragility of the blood vessel walls.

In the normal cycle the function of the spiral arterioles appears to be transitory and cyclical, with much of their extent being cast off during the desquamative phase. It would appear that with hyperplasia, which is a noncyclical lesion, the function of the spiral vessels may be more fixed and prolonged, and this would seem to be indicated by the vascular hypertrophy and hyperplasia which Dr. Schwarz has depicted in his slides.

DR. SCHWARZ (Closing).—Dr. Falls' statement concerning the terrific dose of hormone used in these animals is pertinent. The reason we did this was that we had bad timing in the first series. In the second series we were fortunate enough to hit the right point even with the large doses. I can see a very much better way to do this and I would suggest that we do this same experiment over, particularly with the estrogen; that we give smaller doses over a longer period of time and I think we would get better results.

The question that Dr. Campbell raised—are the changes primarily in the coiled arteries or in those supplying the basal third of the endometrium—is an interesting one. Naturally, viewing only single sections we would find it difficult to say which one was involved. It appears to me that with a general enlargement both are involved. In Fig. 7 I showed that the central mass of tissue must be coiled arteries and I am wondering how, if we expect the normal shedding of the endometrium, those arteries could persist and be re-established. It is more likely, as Dr. Novak said, that in these the arteries are so stable that they did not go to shedding.

VITAMIN A THERAPY IN THE TREATMENT OF VULVAR LEUCOPLAKIA*

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DESPITE all that has been written since Schwimmer in 1877 used the term to identify a similar condition occurring in the mouth, leucoplakia of the vulva has been and still is one of the unsolved problems in medicine.

Of unknown etiology, it presents a fairly uniform appearance. The lesions are characterized by a thickening, dryness, and glossy surface of the skin, associated with grayish-white patches, fissure formation, edema, and at times atrophy and scaling. Microscopically, there is found a hyperkeratosis, varying degrees of acanthosis, and hypertrophy of the rete Malpighii. The areas of the vulva most frequently involved are the labia majora, vestibule, inferior portion of the mons, the perineum, and the perianal skin. Pruritus of varying degree is the symptom most frequently complained of, with burning and pain in the region of the labia and vaginal orifice. Urinary frequency and dysuria are often complicating factors.

Since the cause of leucoplakia has not yet been proved, its treatment must of necessity be somewhat empirical, which accounts for the various and varied types of treatment advocated in the past and still being applied, depending upon the individual physician's concept of the etiology. The end results, as would be expected, have on the whole been disappointing, so much so that the statement has been made that no form of treatment thus advocated and used has given universally satisfactory results. Vulvectomy in all cases is advised by some, primarily as a prophylactic measure against the subsequent development of carcinoma, and only secondarily for the relief of symptoms. Others adopt a middle path, combining medical treatment with surgery. Considering these two latter groups, with so few reported end results verified by a complete and careful follow-up, we are in no position to evaluate the ultimate results following surgery. We are apparently baffled in our attempts to effect a cure in all cases of this disease, even though any or all of the many available types of treatment are employed.

Wolbach and Howe have demonstrated that, in the continued absence of vitamin A from the diet, the most prominent change following this deficiency is a transition in which the normal epithelium in various parts of the body is replaced by keratinized epithelium. In 1922, Evans and Bishop found a persisting cornification of epithelial cells in the vaginal smears of rats which had been previously oophorectomized, during a diet test in which vitamin A was either

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deficient or entirely absent. Relief and even cure of keratosis follicularis (Darier's ichthyosis), and other types of keratotic skin conditions are frequently reported in the literature.

Material

It was in 1942, when confronted with this formidable problem, that we undertook to investigate every patient with a microscopically verified diagnosis of leucoplakia vulvae and the effects obtainable by the use of vitamin A. All patients before starting treatment were given a thorough physical and pelvic examination, and tissue removed from the lesions by biopsy was examined for confirmation of the clinical diagnosis. Routine laboratory tests were made in all cases, including vitamin A determination and gastric contents analysis. With the exception of the gastric contents examination which in approximately 60 per cent of our cases showed little or no free hydrochloric acid, all other tests were substantially negative from a diagnostic standpoint. Compared to the normal physiologic incidence of anacidity of 35 per cent for any similar age group, our figure is definitely abnormally high. Swift described a series of patients with vulvar changes which he attributed to vitamin A deficiency. This important observation is the first intimation of record regarding the possibility of its being of etiological significance in the pathogenesis of leucoplakia vulvae.

Clinical studies in other fields have demonstrated the relationship existing between gastric anacidity and the low plasma level of vitamin A. Premature infants have little or no free hydrochloric acid in the stomach, with a concomitant low plasma level of this vitamin. Nutritional improvement takes place after the administration of lactic acid milk with a proved rise in the vitamin A level. Similarly, in certain diseases of adult life, as in carcinoma of the stomach and in pernicious anemia, the plasma level of vitamin A is low or entirely absent. In both these conditions, there is either complete anacidity or subacidity of the gastric contents.

Considering our negative laboratory findings which have been substantiated by others, vitamin determinations and gastric contents examinations have been eliminated from the routine laboratory check-up in recent cases. However, despite the presence of the normal plasma levels of vitamin A in our patients, we still considered leucoplakia vulvae as being partly due to a subclinical deficiency of this vitamin.

In 1947 the authors made a preliminary report on the use of vitamin A in the treatment of leucoplakia vulvae, at which time eighteen patients were under observation. Up to the present time, forty-two patients have been seen by us and this presentation is based on the results obtained by the use of vitamin A alone, or in combination with another therapeutic agent.

Age.—The age incidence was:

4 patients in the third decade,
17 patients in the fourth decade,
17 patients in the fifth decade,
3 patients in the sixth decade,
1 patient in the seventh decade.

This age incidence does not conform to the extreme limits reported by others. The youngest was 34 years of age. Ten patients had not reached the menopause; in the remaining 32, menstruation had been absent for periods varying from six months to twenty-nine years.

Although it is claimed that leucoplakia vulvae is rare in the Negro race, three of our patients were Negroes.

Symptoms.—The predominant symptoms complained of were:

1. Pruritus of the vulva.
2. Burning sensation of the vulva.
3. Fissures of the vestibule and vulva.
4. Burning sensation on urination.
5. Dyspareunia.
6. Vaginal discharge.
7. Rash of the vulva.
8. Small ulcers of the vulva.

Of these, the symptom most frequently complained of was pruritus of the vulva, especially severe at night.

Treatment

In all patients, vitamin A treatment was begun immediately after the complete examination, supplemented by histological proof. The daily oral dosage varied from 250,000 to 500,000 units and intramuscular injections of 50,000 units given twice weekly. In addition, each patient received fifteen drops of dilute hydrochloric acid (U.S.P.) in water, three times a day with each meal. Diet was regulated and one high in vitamin content was suggested. The immediate response to this type of therapy varied. In some patients the subjective symptoms were relieved within several weeks, while in others it was necessary to increase the amount of vitamin A both orally and by injection, before any appreciable relief was manifested.

With marked menopausal changes, substantiated by vaginal smear examinations, the administration of supplementary estrogens appeared to be helpful. Five such cases are included in this series. Vitamin D in dosage of approximately 5,000 units daily gave variable results. The use of vitamin A and D ointment alone in recent cases did not relieve the symptoms present, but we are using this ointment in conjunction with the oral and injection administrations.

Results

Fourteen patients with proved leucoplakia vulvae were relieved of their symptoms. Tissue examination subsequent to vitamin A therapy showed inflammatory tissue at biopsy with no evidence of leucoplakic changes. Therapy was given over a period varying from four months to three years. The objective improvement seemed to run parallel to the degree of freedom from symptoms. The previously dry, indurated, glossy, and wrinkled external genitals became fuller and the skin became pliable again.

In eight patients, response to vitamin A was practically nil. In reviewing this group the following complicating factors were present: 2 cases of syphilis, 2 cases of diabetes, 1 case of severe cardiovascular disease, 2 patients treated previously with x-ray to the vulva, and 1 who had previously received alcohol injections into vulval tissues.

In patients with chronic systemic disorders or in whom drastic treatment had previously been applied to the vulval tissues, there appeared to be an antagonism to the therapeutic effects of vitamin A. Very slight or no improvement subjectively or objectively followed the therapy in this group.

Five patients were subjected to vulvectomy:

MRS. G.—Under vitamin A therapy with persistence of symptoms, the vulval lesions became worse and vulvectomy was performed in 1946. There has been no recurrence up to the last examination.

MRS. W.—Very extensive involvement of the vulva with severe symptoms. Vitamin therapy was not instituted but vulvectomy advised and carried out in 1945. There has been no recurrence up to her last examination.

MRS. S.—Had vulvectomy in 1939 (before this study was started) with additional tissue removed at two subsequent operations. The operative measures were followed in each instance by a recurrence of the symptoms. With vitamin A therapy her symptoms have been relieved.

MRS. F.—Under vitamin therapy with relief of her symptoms. Apparently there was a recurrence and she consulted another physician who advised and performed a vulvectomy. Six months after this operation she had a recurrence of her original symptoms. She has returned to our clinic for relief.

MRS. A.—Under treatment at our clinic with progressive relief of her symptoms. There was a recurrence and she, too, consulted another physician who advised and performed a partial vulvectomy. Subsequently there was another recurrence and she returned to us for relief.

We have classified thirteen patients under the "interrupted therapy group." Treatment was given over a period of four months to five years. In each instance the symptoms abated under treatment, only to recur at a later interval. However, symptomatic relief was obtained on resumption of therapy when under observation.

Two patients, after preliminary examination and confirmation of the diagnosis after several visits to the clinic, failed to return for further observation. Neither of these patients had received sufficient medication to relieve the symptoms.

Eight patients in this series had complicating rectal involvement. Under vitamin therapy, 5 showed decided improvement, 2 slight improvement, and 1 was unimproved.

In fifteen patients complaining of vulvar irritation simulating leucoplakia, with pruritus as the chief symptom, there was no relief either subjectively or objectively with vitamin A therapy. This group comprised:

Chronic inflammation	6 cases
Kraurosis vulvae	1 case
Paget's disease	1 case
Eczema	1 case
Pruritus undetermined	6 cases

In each instance leucoplakia vulvae was ruled out by tissue examination removed at biopsy.

Comment

Since it was first suggested that vitamin A might be a possible causative factor in the development of vulvar leucoplakia and therefore the symptoms of this disease might be due to a deficiency of this vitamin, no complete detailed report of the end results following this method of treatment has come to our attention. It is our purpose to present such a summation in this presentation. In our preliminary report of 1947, our enthusiasm may have led us to magnify the efficacy of vitamin A therapy. Subsequent experience, based on careful study and follow-up of our patients, taking an unbiased survey of the entire field, has demonstrated that vitamin A therapy is not as reliable as it originally appeared to be. In reviewing the 42 cases under consideration as previously outlined, we can deduce the following:

Fourteen patients with proved leucoplakia, after periods of treatment varying from four months to three years, were not only relieved of their symptoms, but microscopical examination of biopsy specimens taken from the vulva revealed that the former leucoplakia tissue had undergone a transition to an inflammatory type, with no evidence of leucoplakia present.

The time element in the duration of the treatment is an important factor. The need for constant observation over a long period of time with regulation of the dosage to conform to any local tissue changes, the supplementary addition of other vitamins when indicated, the use of hormones or estrogens as occasion arises, and the regulation of diet might be considered by some as a drawback to the use of this method of therapy. Furthermore, the need for constant and careful observation of the patient at regular intervals to detect any signs or symptoms indicating recurrence or malignant changes in the tissue is imperative not only to assure relief of her symptoms but to safeguard her future.

Vulvectomy is the operation most frequently recommended and carried out in patients with a confirmed diagnosis of vulvar leucoplakia. It is claimed that this condition is precancerous and that 50 per cent of all patients subsequently develop carcinoma. In our series no patient developed carcinoma. They were carefully watched to forestall such a contingency and when suspicious signs or symptoms appeared, repeated cytology smears were made and tissue was removed for microscopic examination.

Five patients in our series were subjected to vulvectomy; of these, two were apparently relieved. Three returned with a recurrence of symptoms, plus the characteristic vulval lesions. Sparrow reported a series of six cases of leucoplakia vulvae in each of which vulvectomy was performed; they were under observation from one to seven years. In five patients there was a recurrence of symptoms from various causes. An intraepithelial epithelioma was found in one patient.

It is very difficult to determine with any degree of accuracy how many patients with primary vulvar leucoplakia developed recurrences after vulvectomy, because so few end results after this operative procedure have been reported. From the surgical standpoint, more stress has been placed on the prevention of carcinoma, and rightfully so, than on the less important problem of symptom relief. In other words, vulvectomy at the present time is performed primarily as a safeguard against the development of carcinoma, rather than as a therapeutic measure to relieve local symptoms. Vulvectomy is a mutilating operation and in the case of young women should not be performed without considerable thought and due deliberation.

Eight patients in whom complicating factors were present derived little or no benefit from the treatment. These patients either had a severe chronic systemic disease, or had received local x-ray treatment or alcohol injections into the vulvar tissues. There appeared to be an antagonism to the therapeutic effects of vitamin A in this entire group, the cause of which we are unable to explain.

In thirteen patients treatment was continued at irregular intervals varying from four months to five years. The results subsequent to therapy varied but all of the patients in this group on one or more occasions had a recurrence of their symptoms, despite the fact that they were still under treatment. Here we include those who, due to economic conditions or to living a distance from the hospital, could not attend regularly. These patients usually remained under regular treatment until their symptoms were relieved, then failed to return. In others, insufficient dosage and failure to receive additional medication to correct the deficiency resulted in recurrences. Withholding of hormones or estrogens where needed and neglect by the patient to follow faithfully the dietary routine was also a factor in some. Irrespective of the underlying cause, with the reestablishment of vitamin A therapy the symptoms subsided but recurred at irregular intervals. Two patients with symptomatic relief still showed local evidence of vulval irritation.

Although the symptoms were temporarily relieved while these patients were under treatment, we consider this group to be partial failures. Why these patients should have a recurrence while under treatment constitutes another prob-

lem of which we have no solution, but it is of sufficient importance to warrant further study and clinical investigation.

Fifteen patients with vulvar lesions other than leucoplakia but associated with pruritus did not show any appreciable improvement under vitamin therapy. We may therefore assume from this small series that pruritus vulvae when due to an inflammatory condition will not respond to the administration of vitamin therapy.

We have reviewed our findings following vitamin A therapy in the treatment of leucoplakia vulvae. Considering the small number of patients who were clinically cured and the length of time necessary to accomplish this end, it would appear that no definite conclusions can be drawn regarding the efficacy of this type of treatment, but the symptomatic relief obtained by patients who were made miserable by the intense pruritus and local irritation cannot be disregarded. It warrants further study and clinical investigation of the role played by vitamin A.

No patient in our series while under treatment developed carcinoma. This is in direct disagreement with previous statements and reports.

The relief of symptoms and the marked histological changes in the vulvar tissues following vitamin A therapy are in accord with our belief that vulvar leucoplakia is a manifestation of some metabolic disturbance and that a deficiency of vitamin A is one of the potent factors in its etiology.

Our thanks are due Dr. Oscar Bloom, for his work on the cases in the preliminary report of 1947 which are included in this series.

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Discussion

DR. JOHN I. BREWER, Chicago, Ill.—The authors make several statements that must be classified as superior. They are to be complimented upon their uniqueness and straight-forwardness.

First, they say, "In our preliminary report of 1947, our enthusiasm may have led us to magnify efficacy of vitamin A therapy." That a person or group will bring to us an adverse criticism of their own previously published work is indeed healthy and exemplary. More of this type of thing will materially aid in the search for the fundamental facts of diseases. It also builds a sound foundation for the acceptance of the authors' scientific endeavors.

Second, they add, that subsequent experience has proved that vitamin A therapy is not as simple a problem as it appeared to be, a fact with which we all can agree.

Third, "Considering the small number of patients who were clinically cured and the length of time necessary to accomplish this end, it would appear that no definite conclusions could be drawn regarding the efficacy of this type of treatment." This excellent critical analysis, a good example for all, shows us that they are making strides in the right direction and have not lost sight of basic facts.

In a similar sincere effort to seek out the truth, we may evaluate the relationship between vitamin A deficiency and leucoplakia vulvae in the light of the authors' experience and unbiased report.

That symptomatic relief is obtained in a certain number of patients who are treated with vitamin A is accepted. That vitamin A deficiency is the sole cause of this lesion and that its administration will produce complete reversion to normal of the histologic changes in the skin seems doubtful. The histologic changes brought about by experimental vitamin A deficiency in the human being are not identical to those shown here. Steffen (1940) portrayed the typical findings to be hyperkeratosis, vacuolization of the prickle cells, homogenization and sclerosis of the connective tissue, and atrophy of the dermal appendages. Acanthosis and an inflammatory reaction in the cutis were not part of the process, as they are in leucoplakia vulvae. Furthermore, the changes reverted to complete "normal" after only sixteen days of therapy with vitamin A, in marked contrast to the long duration of treatment required in the series reported here. Complete regression was not obtained in the latter series but, rather, there was uniform persistence of the inflammatory reaction in the cutis. Another point remains to be explained. It is generally accepted that night blindness is the first clinical evidence to appear in vitamin A deficiency. And yet in the cases described there are profound chronic skin changes without any indication of night blindness.

Keratinization does occur in vitamin A deficiency but it is accompanied by other tissue alterations noted above. Keratinization is not typical of vitamin A deficiency alone, since it is caused by deficiencies of biotin, pantothenic acid, riboflavin, nicotinic acid, vitamin C and, possibly, D. This single change cannot be taken as evidence of vitamin A deficiency, in the absence of other signs and symptoms. It may well be, however, that insufficient amounts of any one of these vitamins can be fundamental in producing a secondary A deficiency which, in turn, may induce specific skin changes.

That this vitamin may play a part in the development of atrophic vulvar changes, such as those typified by the condition termed kraurosis, the atrophic stage of leucoplakic vulvitis, or various other designations, is entirely possible. The fact that the blood level of vitamin A is within normal limits may not be disturbing to this postulation as the authors indicate. The ability of the body to utilize vitamin A is as important as its mere presence and it is known that an abundant intake of vitamin E is necessary for such utilization. This tie-in with vitamin E, which is noted for its effect on the epithelium of the genital tract, brings up intriguing speculations as far as vitamins and vulvar lesions are concerned.

The final understanding of the lesion, designated by the authors as leucoplakia vulvae, must await clarification of the etiological role of vitamins, hormones, certain systemic diseases of which generalized skin diseases may be but a part, and above all the unified acceptance of just what leucoplakia and kraurosis are, both clinically and histologically, their relation to each other and to lichen sclerosus et atrophicus. The work presented will play a fundamental part.

DR. FREDERICK S. WETHERELL, Syracuse, N. Y.—Dr. Hyams and his co-workers have been making a study which is much more complex than it would seem to be at first glance.

The dosage of vitamin A used by the authors is from 25 to 50 times that of the usual dose found in good pan-vitamin capsules. This should be remembered when complete failures are reported by the few who have tried vitamin A therapy in leucoplakia vulvae.

The statement that, despite the proper plasma levels of vitamin A, there may still be a subclinical deficiency is a fair one. We still do not know enough about the vitamins and their actions.

The determination of free hydrochloric acid in stomach contents is dependent upon so many factors, including that of the method used, that it may well be left out of their calculations, as the authors have done in their recent cases. For example, the statement that 60 per cent of their cases showed little or no free hydrochloric acid as compared to a normal physiologic incidence of anacidity of 35 per cent for any similar age group has little significance when compared with the statement of Winkelstein that the incidence of true achlorhydria, unassociated with organic disease, is 1.2 per cent and, therefore, rare in normal individuals of both sexes, regardless of age.

It is to be noted that the authors added vitamin D to their therapy and also used vitamin A and D ointment alone in recent cases. And, too, estrogenic substances have been exhibited at times.

As is usual in clinical investigations on human beings, as compared with animal experimentation, there is a tendency to become empirical. Relief of the patient's symptoms is paramount in the clinician's mind. The scientific method gives way to the importuning of the clinician's background. Hyams has given us a valuable lead. Further studies by members of this association may finally solve the problem of the etiology of leucoplakia, whether it be of the vulva or other mucocutaneous areas of the body.

DR. JOHN PARKS, Washington, D. C.—The diagnosis of leucoplakia may be very misleading. Allergic dermatitis, psoriasis, and lichen planus may be difficult to differentiate from leucoplakia. However, after these skin conditions are ruled out, leucoplakia of the vulva remains as a disease which has many components. Dr. Hyam's slides illustrate two patients with lesions which are very similar in external appearance and by microscopic studies. The first patient has a metabolic disorder in which kraurosis and leucoplakia are both present. She has been operated on three times for removal of areas of leucoplakia. During the past five years multiple vitamin therapy and dilute hydrochloric acid have prevented further recurrences. When systemic therapy is discontinued a truly acute vulvitis blossoms out again. The second patient has a compulsive neurosis of twelve years' duration which has led her to chronic traumatization of the vulva. She has had all types of local treatment, even unnecessary exposure to x-ray therapy. Psychotherapy is the first therapy to which she has made any response. In a study of leucoplakia of the vulva, metabolic factors are extremely important; the role of compulsive self-inflicted vulvar trauma is often difficult to evaluate, and the contributions which secondary infection make to skin changes vary immensely.

MR. CHARLES D. READ, London, England.—I was much interested in Dr. Hyams' presentation. The first time I had brought to my attention the possibility of hydrochloric acid deficiency and a vitamin deficiency in leucoplakia was at the reading of a paper twenty years ago by Brian Swift of Adelaide, Australia. So far as I can recall, the claim was that this therapy only helped the actual irritation. Unlike Dr. Hyams, I have seen two cases proceed to epithelioma of the vulva during the course of this type of therapy. I wonder if by relieving the symptoms of leucoplakia we are not lulling ourselves occasionally into a false sense of security. It seems to me that if we are not careful we may have the unfortunate experience of having a patient under such treatment while she is actually developing epitheliomatous change.

The second point, that of the question of terminology, as pointed out by Dr. Brewer, is extremely good. Some years ago, Dr. Taussig gave his paper and he compared leucoplakia with kraurosis. I insist that they are two separate diseases. Kraurosis never ends up as an epithelioma; leucoplakia may or may not. You may end up with a stenosed introitus and apparently a spontaneous cure on occasions.

I have had the unpleasant experience of seeing epitheliomatous change develop upon a leucoplakia while the patient was awaiting admission to the hospital. I am not criticising

Dr. Hyams. I do not think there is much possibility of his missing carcinoma of the vulva. However, I do suggest that it would be better for the patient if we treated leucoplakia surgically and gave it the importance that it deserves.

DR. HYAMS (Closing).—At a meeting of the New York Obstetrical Society held several years ago, Dr. Norman F. Miller presented a very elaborate review of his study of leucoplakia vulvae. The feeling at that meeting was that vulvectomy was the treatment of choice on account of the malignant potentialities. That same feeling seems still to prevail among most gynecologists.

It is significant that malignancy was not encountered in any of our cases, notwithstanding a very careful follow-up. Why this should be we cannot say, except that leucoplakia vulvae and vulval carcinoma can occur in the same patient as individual conditions.

Dr. Parks believes as we do that leucoplakia vulvae is a result of some metabolic disturbance, the exact cause of which we do not know.

Vulvectomy does not appear to be the therapeutic solution of this most annoying condition.

While vitamin A, in the treatment of leucoplakia vulvae has some drawbacks, the benefits derived as outlined in this presentation warrant further study.

PATHOLOGICAL ASPECTS OF HYDATIDIFORM MOLE AND CHORIOCARCINOMA

EMIL NOVAK, M.D., BALTIMORE, MD.

(From the Department of Gynecology, Johns Hopkins Medical School)

AS A basis for the views expressed in this paper I have recently reviewed 70 cases of hydatidiform mole and 30 cases of choriocarcinoma from the material of our laboratory. I need scarcely say that in the greater portion of these cases slides or tissue were sent in from outside clinics. This would probably be evident from the disproportionate number of malignant lesions in this group. A good many other cases which I have had the opportunity to study pathologically have not been included in this review because of the poor quality of the material or the insufficiency of clinical data. The clinical aspects of these two lesions will not be included in this discussion, especially as a goodly fraction of the cases studied are from the material of the still rather young Mathieu Memorial Chorionepithelioma Registry, so that the follow-up studies, so essential in the clinical investigation of lesions of this type, are not as yet possible. A more complete study than is as yet possible will be published later under the auspices of the Chorionepithelioma Committee.

To restrict this discussion of hydatidiform mole and choriocarcinoma to their pathological aspects does not limit it as much as might at first thought appear. After all, the purely clinical features of these two chorionic diseases are reasonably well known. These are dependent upon the pathological characteristics of the two diseases, but only if we envisage pathology as including the living, biological characteristics of both the fetal and maternal tissues concerned in these lesions. This statement at once sets forth one of the chief theses of this paper.

In the consideration of most tumors this living pathological consideration is far less important than it is in the interpretation of trophoblastic lessions. With the ordinary forms of epithelial neoplasms, one can utilize the static histological features as a reliable means of distinguishing the benign from the malignant, with little or no regard for the vulnerability of the invaded tissue, which is taken practically for granted. Totally different, as I shall try to show, is the problem as regards lesions of the trophoblast, a tissue which is normally invasive, while the invaded maternal tissue, and perhaps the maternal systemic organism, normally exhibit varying degrees of resistance to the invading elements. In this field, therefore, simple morphological considerations are of far less importance than they are in other pathological problems.

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I do not believe that this consideration has been sufficiently appreciated by those who have attempted systems of classification. These have been based almost entirely on the structural and quantitative characteristics of the party of the first part, represented by the trophoblast, without due regard to the defensive mechanism of the party of the second part, and also without due regard to the invasive propensities of the trophoblast in normal pregnancy.

After all, it is the destructiveness of the trophoblast which makes implantation possible. Its contact with the endometrium is the kiss of death, and, once beneath the surface, the trophoblast continues its destructive effect upon the blood vessels, setting free the maternal blood which now takes over its function of nourishing the parasitic ovum.

It is worth noting that during this early phase, when the trophoblast exhibits destructive properties just as marked as those of a choriocarcinoma, there are none of the histological cell changes which pathologists ordinarily look upon as the structural evidence of such destructive propensities. I emphasize this point because I believe that it minimizes the indispensability of so-called anaplastic changes in the diagnosis of malignant trophoblastic lesions, using the term malignant in both a clinical and a histological sense.

As a matter of fact, the trophoblast in this early phase possesses in quantitatively lesser degree practically all the properties of a choriocarcinoma. It actually destroys maternal tissue just as does the latter, though this property appears to be lessened as soon as the villous apparatus is established. But the capacity to invade maternal tissue is not lost, being seen throughout pregnancy. This is evidenced not only by the trophoblastic outgrowths from the villous surface, but also by the invasion of not only the decidua but also the uterine musculature by the so-called chorionic or trophoblastic wandering cells. The exact nature of these cells is still a point of discussion, especially as to whether they are of syncytial or Langhans cell type. From the standpoint of mere histological appearance, it would seem possible that both trophoblastic layers may be involved in this infiltration, and in some cases the infiltrating cells appear to be of intermediate type. This would not be surprising, since the syncytium itself is a derivative of the cytotrophoblast. There are many embryologists who believe that the trophoblastic infiltration of the uterine wall is due to the ameboid properties of the invading cells.

The degree of this trophoblastic-cell invasion is very variable, but it is often very pronounced in the implantation area. Its practical significance lies in the fact that it has often led to the incorrect diagnosis of choriocarcinoma. It is present not only in entirely normal pregnancy, but also in cases of benign hydatidiform mole. Many times I have been sent sections of uteri which, for one reason or another, had been removed after the evacuation of a hydatidiform mole, and in which the surgeon probably congratulated himself because the pathologist, on the basis of chorionic cell infiltration of the uterine wall, had reported choriocarcinoma, not appreciating the entire normality of this invasiveness. This error is exceedingly common, as is already apparent in the material of the Chorionepithelioma Registry. It is easy to see how the statistics of choriocarcinoma can be, and actually have been, vitiated by the inclusion of cases thus wrongly diagnosed.

There are two chief points of difference between the normal trophoblastic invasion of the uterine wall and that seen in choriocarcinoma. In the former the cells infiltrate along the tissue spaces singly, and they exert none of the destructive or lytic effect upon the uterine muscle which the earlier trophoblast or the cell masses of choriocarcinoma inflict upon the maternal structures. Not only do the infiltrating cells stain sharply and clearly, but so does the uterine muscle in which they are scattered.

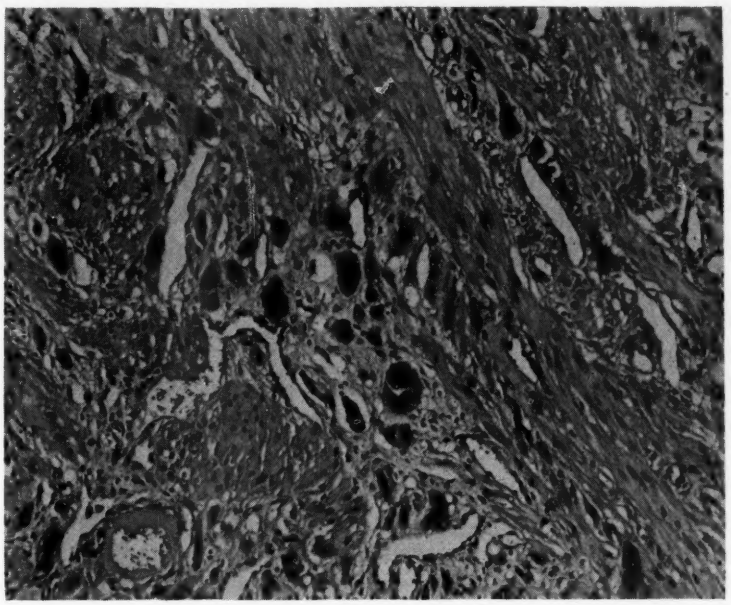

Fig. 1.—Trophoblastic invasion of uterine muscularis in normal pregnancy.

By contrast the invasion of the uterine wall in choriocarcinoma is in the form of large columns or masses of trophoblast which advance into the muscle, killing it as they advance, so that coagulation necrosis and hemorrhage are always seen. Other differences, such as possible anaplastic changes in the invading masses of chorionic epithelium are also sometimes noted, but these will be commented upon later in this paper.

Not only the uterine musculature but also the decidua may show this "cytotypic" invasion of trophoblastic cells, as it was called by Meyer,[1] rather than the bulky infiltration of trophoblast characterizing chorionepithelioma. The normal infiltration of the decidua with trophoblastic cells varies greatly in degree and often seems to be very slight or absent, but it has led to frequent confusion in diagnosis. It has two chief diagnostic connotations. The examination of material obtained by curetting after hydatidiform mole may show such pronounced trophoblastic infiltration of the decidua and muscle as to lead to the diagnosis of choriocarcinoma and impel the surgeon to radical operation. In cases of this sort examination of the removed uterus shows, not choriocarcinoma, but simple trophoblastic infiltration of the decidua, with often similar infiltration of the muscularis. Practically always there is associated inflammatory infiltration of the decidua.

It is this group to which the term syncytial endometritis is often employed, and I believe correctly, though a better one would perhaps be syncytial deciduitis. This particular lesion, especially when the infiltration of syncytium is marked, has in past years often been wrongly designated as syncytioma, a term originally applied by Marchand[2] to indicate the so-called atypical variety of choriocarcinoma. However, the infiltration is limited to the decidua, except for the cytotypic infiltration of the muscularis sometimes associated. It represents only a residuum of trophoblast in the decidua, with inflammatory changes in the latter, and it is not neoplastic. In my experience it is this lesion, syncytial endometritis, which more frequently than any other has been mistaken for choriocarcinoma.

Still another pseudomalignant attribute of trophoblast, depending upon its destructiveness, is its capacity to break through the walls of blood vessels, so that trophoblastic cells find their way into the circulation for deportation to distant organs, particularly the lungs. The normality of this deportation was established by Schmorl as far back as 1893. It constitutes a normal or physiological form of metastasis, and it gives rise to an interesting secondary question which cannot yet be answered. I refer to the fate of such deported villi or trophoblast. Certainly these must undergo rapid regression, as indicated by the fact that pregnancy tests become negative so soon after delivery. But other tissues, such as endometrium, can take root in the lungs, if one can draw such a conclusion from the experiments of Hobbs and Bortnick[3] on rabbits. Does this not indicate some sort of systemic antitrophoblastic defense mechanism? I believe that such a mechanism must exist, although, in spite of scattered work along this line for many years, we are entirely ignorant of what this protective force may be.

In cases of histologically as well as clinically benign hydatidiform mole, villi as well as trophoblastic tissue may be transported to the lungs, and these likewise appear usually to regress promptly and completely. Nor do they give any clinical or x-ray evidence of their short-lived existence. However, I recall a case of benign mole in which the patient, some days after the evacuation of a mole, had a moderate hemoptysis, expectorating a tablespoonful of blood, with no previous pulmonary symptoms and with negative x-ray plates of the chest. This was before the days of biological tests. While this hemoptysis was somewhat disturbing, no further untoward symptoms developed, and the patient has remained well for more than twenty years, after having passed through several normal pregnancies since she had her mole.

While spontaneous and rapid regression of such transported trophoblastic tissue must be the rule, there are apparently rare exceptions in which it may become neoplastic, giving rise to ectopic choriocarcinoma. However, in cases of this sort it is often difficult to exclude a primary choriocarcinoma in the uterus, since it is certainly true that such a uterine lesion can completely regress and disappear locally, while the patient goes on to die of metastases, as will be discussed later.

Even in cases of unquestioned choriocarcinoma with extensive metastases to the lungs as well as other organs, examination of the pulmonary metastases often shows evidences of regression. I have had the opportunity of studying autopsy material of this sort in a considerable number of fatal cases, and I have in some

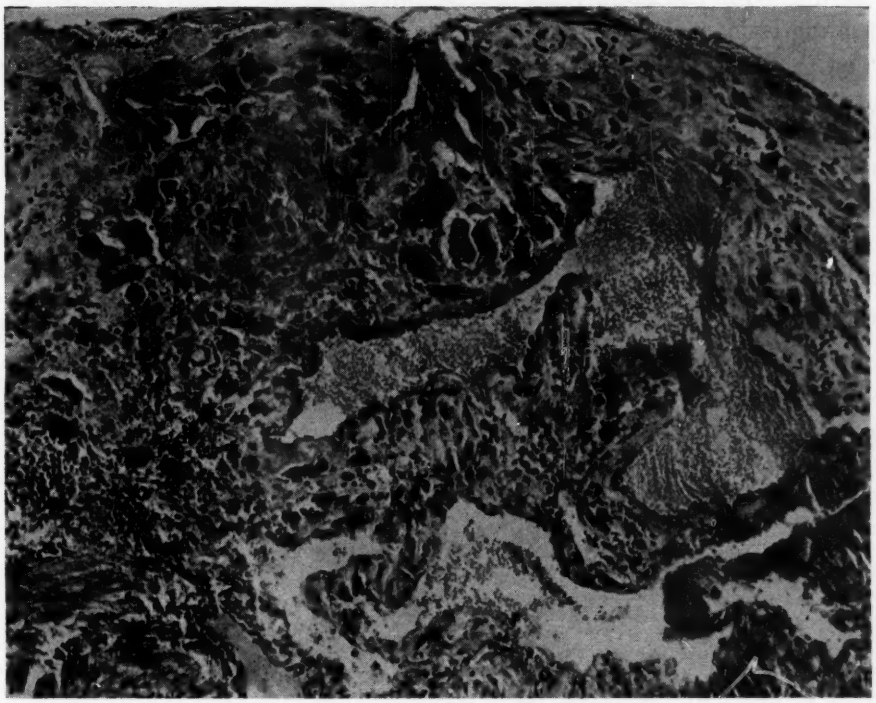

Fig. 2.—So-called syncytial endometritis. Such trophoblastic infiltration is not neoplastic, and is often seen, though in varying degree, with normal pregnancy and benign hydatidiform mole. This section comes from a normal pregnancy terminated by Porro operation because of large multiple myomas at the age of 41 years.

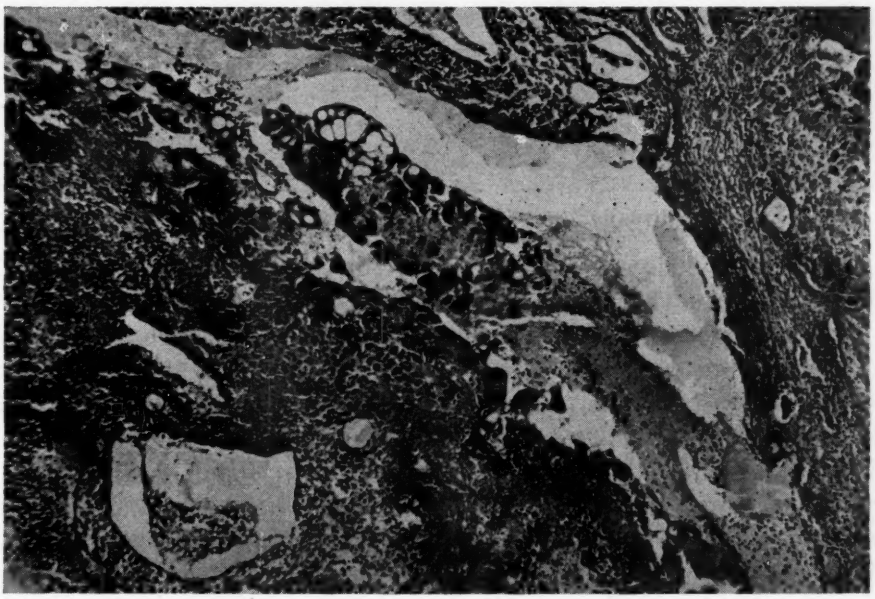

Fig. 3.—Syncytial endometritis seen in curettings some weeks after evacuation of benign mole. Note the vacuolated syncytium in the large trophoblastic mass lying free in center of field, with scattered trophoblastic cells above and to right.

been struck with the apparently degenerated and regressive character of some of the lung lesions, if histologic appearance may be taken as a guide.

The fact that even the trophoblast of normal pregnancy has a tendency to penetrate the blood vessels to some extent, as does that of clinically benign hydatidiform mole, makes it easier to understand the occasional intensification of this vascular penetrability which characterizes certain moles which otherwise are histologically in no way different from those in which this penetrative tendency is much more restrained. This is an extremely important point to stress, since it is just this intermediate type of mole which has given rise to a very con-

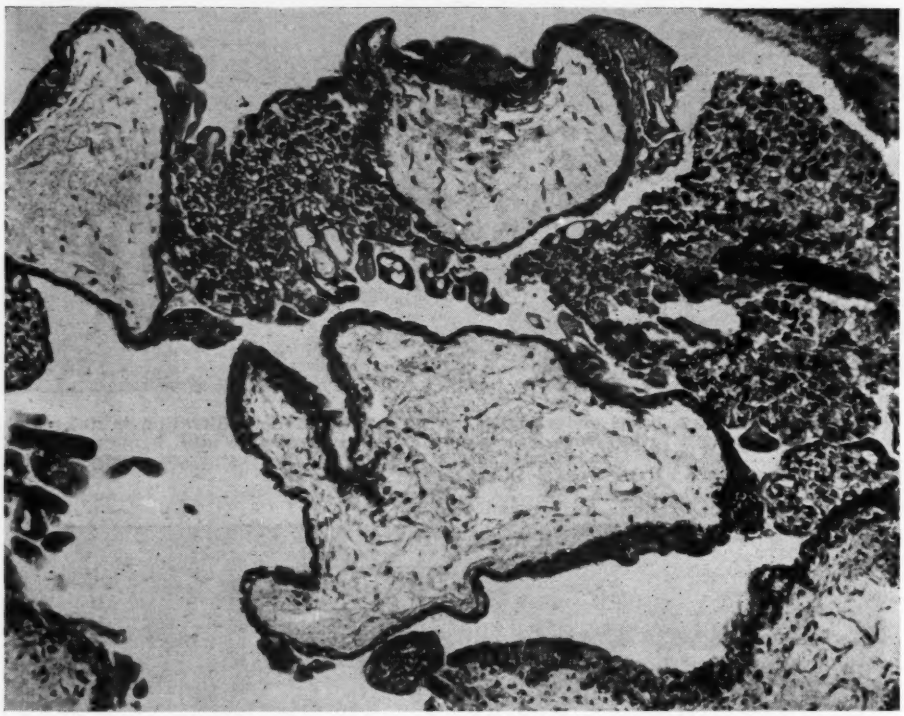

Fig. 4.—Benign hydatidiform mole with moderate trophoblastic overgrowth.

fusing literature. This group has been variously designated as malignant mole, destructive mole, or chorioadenoma destruens. The latter term, originally applied by Ewing[4] (1910), has been quite widely adopted, though it has seemed to me to be a very poorly selected one. Ewing himself chose it because of an assumed comparability of the villi with gland structures. Neither histologically nor functionally does such a comparison appear valid. The chorionic villi resemble more nearly the villi of the intestine rather than the glands, and the covering epithelium, like that of the intestinal villi, exhibits such functional properties as diffusion and osmosis, selective filtration, and secretory activity.

The difference between the "malignant" mole and the benign one, then, in addition to a more marked trophoblastic proliferation, lies in the fact that in the former the intravascular invasion which characterizes even the normal trophoblast is abnormally great, while the cellular characteristics may be, and, in my experience, have most often been identical. A better designation for this group, therefore, would be penetrative or destructive mole. To call them malignant is

misleading, because they do not ordinarily produce distant metastases, as does the really malignant chorionic lesion, the chorionepithelioma, and they are always cured by hysterectomy. It is true that the histologically benign penetrative mole may extend through the thickness of the uterine wall to the peritoneum, with serious and perhaps fatal intra-abdominal hemorrhage as a result. But these clinically grave possibilities are, nevertheless, in cases of this small group, produced by a lesion which, from a histological standpoint, is in no noteworthy way different from clinically benign moles. The difference lies in a greater invasiveness of a benign tissue, somewhat comparable to the often extensive invasion of the uterine musculature by normal endometrium in adenomyosis.

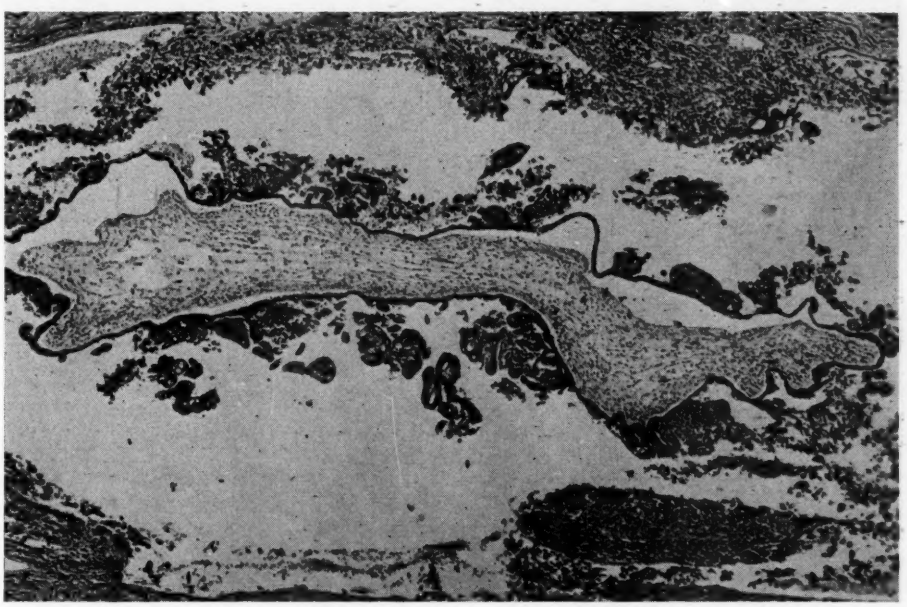

Fig. 5.—Only slight trophoblastic proliferation in a benign mole which penetrated deeply into the uterine wall and vessels.

Many of the leading students of the problem (Chaletzky, Marchand, Kaufmann, Fraenkel, Neumann, Pick, and others) look upon trophoblastic overgrowth as essential to the pathological diagnosis of hydatidiform mole, whether or not it is a primary or secondary change in so far as etiology is concerned, and this would represent my own reaction to the problem. The proliferation may be of moderate degree or it may be extremely marked, with large tongues usually of both trophoblastic layers pushing out into the musculature, although the latter shows no evidence of the destructive or lytic effect produced by the invasion of trophoblast in the early stages of implantation.

A working rule which I have formulated for myself is that, in the presence of a well-marked villous pattern, with a sharply demarcated margin between the stroma and the trophoblast, a mere quantitative excess of the latter, no matter how pronounced, does not justify a diagnosis of choriocarcinoma. So far I have encountered no case in which subsequent developments have seemed to belie the reliability of this rule. Incidentally, mitoses are infrequently seen in cases of this type, as are other evidences of undue anaplastic activity.

Hertig and Sheldon,[5] in a recent study, have attempted a system of histological classification of moles based on such purely morphological considerations as the amount of trophoblastic proliferation and the presence or absence of evidences of what they designate as anaplastic change, admittedly far more difficult to establish with lesions of this sort than with other tumors. They divide their cases into six groups, as follows: (1) benign, (2) probable benign, (3) possible benign, (4) possible malignant, (5) probable malignant, (6) malignant.

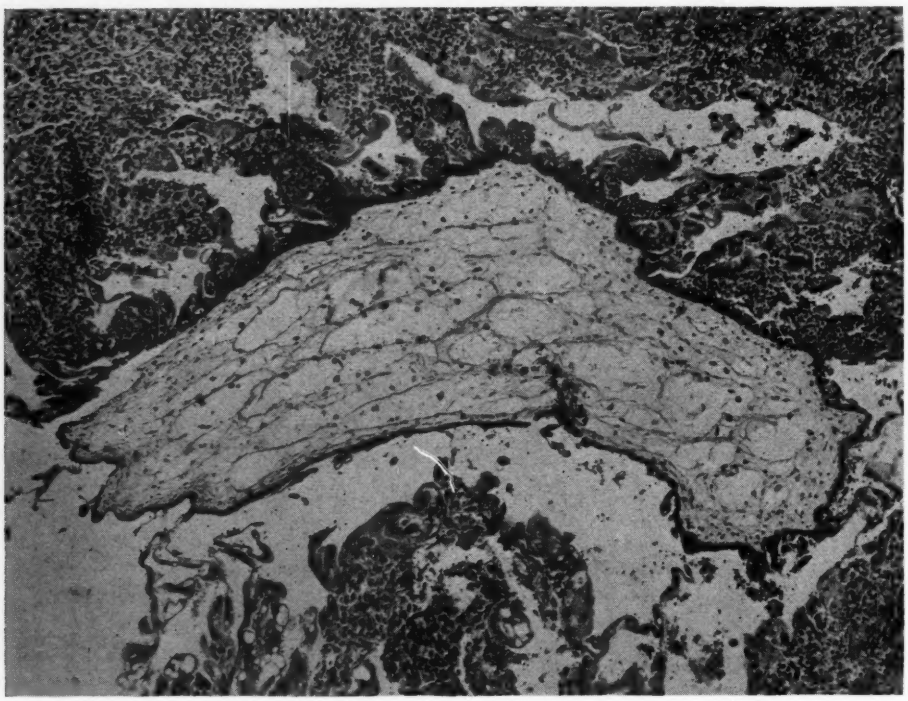

Fig. 6.—Marked trophoblastic overgrowth in so-called chorioadenoma destruens. Hysterectomy was done in this case, with no recurrence after several years.

It is difficult to believe that such delicate nuances of differentiation will be of practical value, especially since most pathologists have only infrequent opportunities to examine molar tissues. As a matter of fact, the attempt to pigeonhole the pathological diagnosis in any such fashion is sure to lead to unnecessarily radical surgery in some cases. I have already encountered instances in which this has occurred, the mole having been fitted into the possible or probable malignant group on the insecure basis of the descriptions given by Hertig and Sheldon. As a matter of fact, I have repeatedly seen the histological pictures described by these authors in moles which clinically have been entirely benign.

In spite of their insistence on these fine differentiations, it is of interest that all of the patients in their group of 200 have remained well except the small group of five obvious choriocarcinomas. It appears to me to be rather hazardous to make such gratuitous assumptions of histological malignancy with no clinical support other than the occasional development of the so-called chorio-

adenoma destruens, itself a poorly defined group which depends largely on personal evaluation unless the lesion is of the penetrative intravascular type which has already been discussed.

It is not in the latter sense that Hertig and Sheldon use the term. Furthermore, the existence of the so-called chorioadenoma destruens cannot be demonstrated until after removal of the uterus, impressions based on evacuated molar tissue being of little value in this respect. The examination of curetted tissue after expulsion or evacuation of a mole likewise possesses very limited significance, though concededly more than that of the usually degenerated molar tissue which often fills the uterine cavity.

The penetrative variety of mole is relatively uncommon, but it does seem to constitute a special group, in that it may lead to extensive infiltration of the uterine wall, with often considerable enlargement of the uterus, and, in spite of the absence of distant metastasis, to death from either external or intra-abdominal bleeding. But other intermediate types of so-called chorioadenoma, as the term is used by Hertig and Sheldon, as well as others, are far more difficult to define. It is quite likely that there are degrees of cancer potentiality in hydatidiform mole, but I do not believe that these can be determined by the simple histological criteria suggested by Hertig and Sheldon.

These authors emphasize such criteria to warn pathologists as to their possible ominous significance, while Ewing, on the other hand, expressed a different purpose in trying to delineate as an intermediate group the malignant or destructive mole which he designated as chorioadenoma destruens. He says, "The grounds for separating the destructive placental polyp [meaning chorioadenoma destruens] from other forms of the typical chorioma are chiefly practical ones. It makes much difference to the clinician and to the patient whether the laboratory diagnosis carries with it a necessarily hopeless prognosis or a chance for recovery, and it is just because the average destructive polyp offers a hopeful prognosis which some other typical choriomata do not, that specific terms are desirable." As I see it, Ewing's emphasis on a special group of intermediate cases is meant to be an aid to prognosis after hysterectomy, justifying a far more hopeful prognosis than can be expected in the genuine choriocarcinoma.

A first reading of the paper of Hertig and Sheldon is likely to be confusing and rather startling in that 59 of the 200 cases in the series are designated as malignant. A more critical review, however, indicates that the "malignancy" of these 59 cases is based upon such criteria as the amount of trophoblastic proliferation and the degree of anaplastic activity. It seems obvious that this large group of "malignant" cases includes many cases of chorioadenoma destruens and many moles which other pathologists would classify as markedly proliferative but benign. It must be emphasized, however, that metastases never occur in cases of this type, and that they are always curable by simple hysterectomy. This is certainly not true of choriocarcinoma, which by long usage is the designation for the truly malignant trophoblastic tumor which does metastasize, often very early and very widely, and which usually causes death.

This does not mean that only tumors which kill the patient are to be called malignant, for the histological characteristics of the malignant choriocarcinoma

are totally different from all but five of the "malignant" group segregated by Hertig and Sheldon. In this small group of five, incidentally the only ones which terminated fatally, the histological picture was the one which would be accepted by all pathologists as genuine choriocarcinoma. Again, it may be emphasized that the diagnosis of malignant choriocarcinoma does not depend upon the grave and usually fatal course but upon the characteristic histologic picture. As a matter of fact, not all cases of choriocarcinoma end fatally, and Fig. 8, showing a histological appearance in no way different from that of numerous fatal cases, but very different from many of the "malignant" cases of Hertig and Sheldon, is from a patient who is living and perfectly well four years after operation.

I am well aware that suggestions for improving the nomenclature of this whole group of lesions have been made, and that some believe that the intermediate group should be looked upon as choriocarcinomas of a more highly differentiated but less malignant type. Thus far the evidence appears to me to indicate that they are perhaps better to be interpreted as highly proliferative types of benign hydatidiform mole, and that the latter is possibly to be regarded as not a neoplastic but a degenerative process.

Notwithstanding the criticisms which have been made as to the classification criteria of Hertig and Sheldon, their conclusions as to the clinical management of such cases are very sound, and this may impress the average reader as rather surprising in view of their application of the designation of "malignant" in the body of their paper. The danger in their classification lies in the fact that it is offered as a guide to the clinical management, in spite of the fact that it is based on the very incomplete and unreliable evidence of evacuated or curetted material, which rarely gives one an accurate picture of the extent and nature of the lesion as it involves the uterus. It is the latter picture which usually permits of full evaluation.

This of course does not mean that hysterectomy should be the routine treatment of hydatidiform mole, for it is necessary in only a small proportion. If the evacuated or molar tissue shows only a moderate degree of trophoblastic overgrowth, the clinical course is usually smooth in that bleeding ceases, and the biological tests soon become negative. I have had the opportunity of examining the uteri of many patients on whom the surgeon has performed hysterectomy in spite of the innocent histological appearance of the original molar tissue.

Perhaps for this reason I have not been at all frightened to find in such cases not only residual hydatidiform villi, but also marked trophoblastic overgrowth, with even at times a sprinkling of mitotic figures in the cytotrophoblast. I am convinced that the majority of patients with such findings would have remained well after thorough curettage. But a good many of them would have shown a persistence of positive pregnancy tests for long periods of time, even for many months. Under such circumstances most gynecologists will feel fully justified in proceeding with hysterectomy, since secondary choriocarcinoma is always a possibility, though its incidence is far less than was formerly believed to be the case. After all, hydatidiform mole is only moderately rare, but choriocarcinoma is so extremely rare that in some fairly large clinics no case has ever been

encountered. I, personally, believe that the sequence does not occur in much more than 1 per cent of cases, the larger incidence reported by some being due to errors in the histological diagnosis of choriocarcinoma.

While the persistence of a strongly positive test, especially when associated with bleeding, and an enlarged, subinvoluted uterus is a valid indication for hysterectomy, the examination of the removed uterus will fail to show choriocarcinoma in all but a small proportion of cases. Sometimes it reveals residual vesicular tissue if the curettage has not been thorough. In most such cases in which the curettage has been thoroughly done the microscope will show hydatidiform villi deep in the uterine wall beyond the reach of the curette. These often show marked trophoblastic overgrowth, or considerable masses of trophoblast without villi may be found in the lumina of vessels, or there may be a persistence of chorionic wandering cells in the myometrium or in the form of the so-called syncytial endometritis which I have already discussed, and which is not neoplastic. But any of the residua may keep up a positive pregnancy test though none of them is malignant, and though they would unquestionably regress in all but a few cases. But this is the rub, for in a small proportion choriocarcinoma may subsequently arise, and it is this hazard which fully justifies the hysterectomy.

Again, in some cases the histological examination of the removed uterus may show extensive invasion of the trophoblast, but with a well-preserved villous pattern, with or without a strong intravascular growth tendency, but with no destruction of uterine muscle. It is in this group that pathologists will differ, and it is this group which Ewing obviously had in mind in coining his term of chorioadenoma destruens, simply to separate it from frank choriocarcinoma. He emphasizes the favorable outlook of these cases, and with this view I am in full accord. And yet it is this group which has so often been diagnosed as choriocarcinoma, explaining the low incidence of deaths in some studies of the latter disease, from which Ewing himself says he has never seen a cure, although there is no doubt that in a small proportion of unquestioned cases cures have occurred.

The point of this whole discussion is that the line of treatment, and especially whether or not to resort to hysterectomy, should be influenced far less by the histological appearance of extruded or curetted molar material than by the clinical and laboratory features which I have already mentioned. An obvious exception to this would be the rare instances in which the curette yields large amounts of trophoblast, with often anaplastic characteristics, but with no trace of villi, and which I believe justify the diagnosis of choriocarcinoma. While the diagnosis of choriocarcinoma from curettings, especially that of the intramural type, certainly is not always possible, it has never failed of confirmation in the small group of cases I have observed in which the curetted material showed the characteristics enumerated above.

Whatever one may feel as to the neoplastic or nonneoplastic nature of the invasive type of mole, no one will dispute the genuinely neoplastic character of the malignant prototype, choriocarcinoma. The work of Marchand in 1895 not only established the epithelial nature of this form of cancer, which Sanger[6] and others had looked upon as a sarcoma of the decidua (sarcoma deciduocellulare),

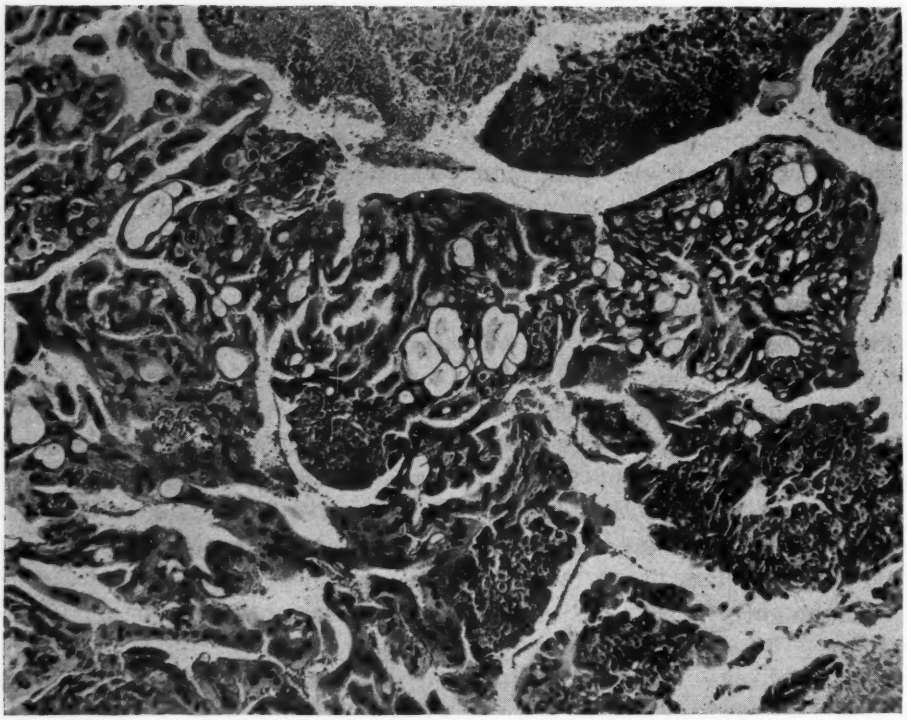

Fig. 7.—Curettings from a case of choriocarcinoma showing large masses of trophoblast and no villi. Diagnosis from curettings is possible in only a proportion of the cases.

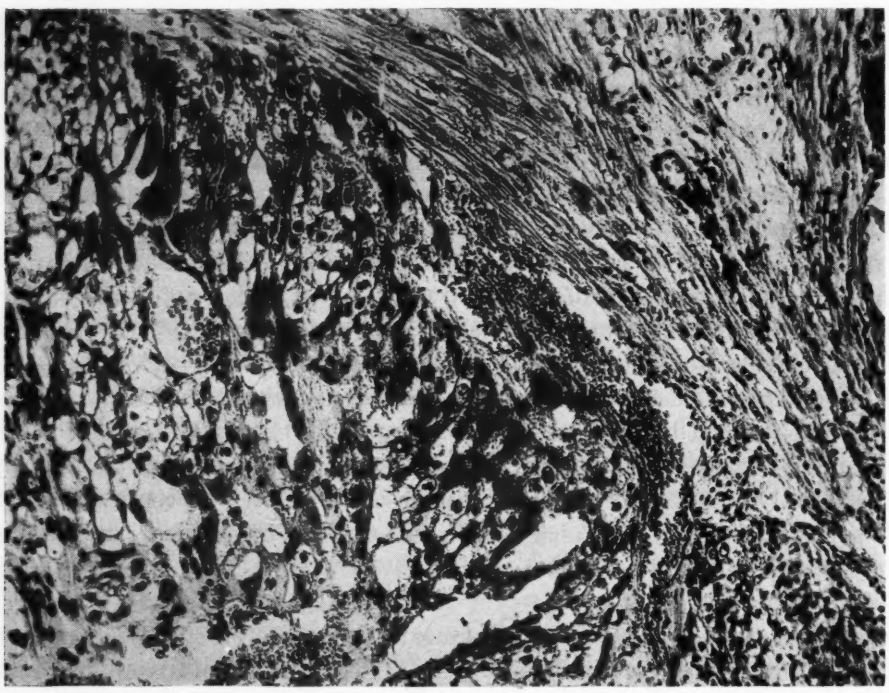

Fig. 8.—Choriocarcinoma invading uterine wall extensively in case shown in Fig. 9.

but also its origin from the trophoblastic epithelium. It must therefore be looked upon as a carcinoma arising from the villous epithelium, much as an epidermoid carcinoma, for example, arises from the stratified squamous epithelium of the cervix.

There are limits, however, to its comparability with ordinary carcinoma. It must never, for example, be forgotten that choriocarcinoma is not a uterine tumor, but a fetal tumor growing in the uterus. We thus deal, as it were, with a tumor of one individual which invades the tissues of another, a relation quite different from that pertaining to most neoplasms. Just what significance this has no one can say, but it is conceivable that it may be important.

Again, it is always to be borne in mind that the invaded organ is by nature endowed with the capacity of resisting the encroachment of trophoblast, as has already been emphasized. This resistance is not ordinarily sufficient to hold in check the heightened invasiveness of malignant trophoblast, but in at least a small proportion it is. A considerable group of cases is recorded in which the uterus has completely thrown off the choriocarcinoma, the genuinely malignant nature of the original uterine growth being attested by the fact that the patient has died from extensive metastases. Such a case was reported by Novak and Koff,[7] who collected a considerable number of similar instances from the literature.

Again, I have already mentioned that in the study of autopsy material from fatal cases of choriocarcinoma I have often been struck with the apparently retrogressive picture presented in some of the metastatic foci, especially in the lung. I shall not belabor this question further, because we know practically nothing as to the nature of the maternal defense mechanism against trophoblastic invasion. However, I believe that this must always be reckoned with, and that it probably explains some of the vagaries of this disease.

The histological picture presented in frank choriocarcinoma is quite distinctive, and not many mistakes will be made in the diagnosis. While "false negatives," so to speak, should be rare, it is the "false positives" which have created such confusion in the evaluation of cases. I mean by this that the diagnosis of choriocarcinoma has in innumerable cases been made in cases of benign mole, syncytial endometritis, and even entirely normal pregnancy. I could cite a great array of such instances from my personal observation, and our still young Chorionepithelioma Registry is already rich in evidence to this effect.

The presence of large masses of trophoblastic cells of both types but in varying proportion, with often mitoses and other anaplastic manifestations which are more easily demonstrable in the Langhans cells than in the syncytium, the necrosis and hemorrhage, and the almost invariable absence of villi—all these make a pattern difficult to mistake, and quite different from the benign choriomas already described. Whether rightly or wrongly, I always lean away from the diagnosis of choriocarcinoma in the presence of well-formed villi, almost regardless of the amount of trophoblastic overgrowth. I have never observed definite villi in a choriocarcinoma whose malignancy has been established beyond all doubt by extensive metastasis and death. I have no doubt

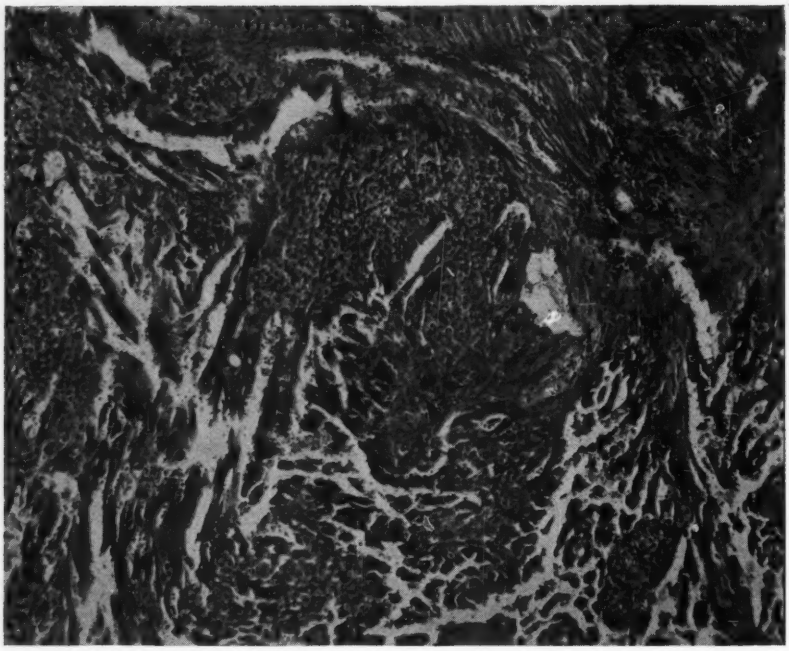

Fig. 9.—Choriocarcinoma, with rather rapid metastasis and death, showing both types of trophoblastic cells, and complete absence of villous pattern. Large areas of cytotrophoblast are seen above and to left.

Fig. 10.—Vaginal metastasis in case depicted in Fig. 7.

that in an occasional case villi may persist in isolated areas of transition from the normal or hydatidiform villi from which such tumors have their origin, but the occurrence must be rare. This is not an expression of a purely personal diagnostic prejudice, for a good many other investigators, including Robert Meyer, also stress this characteristic absence of villi.

Again, to revert to my own experience, I have never seen a choriocarcinoma which was made up of syncytium alone, corresponding to the atypical variety of choriocarcinoma described by Marchand. The latter's original paper is not sufficiently illustrated to lead us to conclude that he wrongly placed in this group cases which we do not now consider neoplastic, but I believe that this must be the case.

Summary and Conclusions

In the pathologic study of hydatidiform mole and choriocarcinoma, one must never lose sight of the fact that the early trophoblast of normal pregnancy exhibits certain characteristics quite like those of cancer. It infiltrates and destroys the maternal tissue, and it even exhibits a physiological type of metastasis in the form of villous and trophoblastic deportation to the lungs. On the other hand, and unlike cancer, the normal restriction of trophoblastic inroads into the uterus and the regression of deported trophoblast can be explained only on the assumption of a local and probably also a systemic defense mechanism, though we know practically nothing as to its nature. Such a defense mechanism, however, may well explain some of the vagaries of choriomatous tumors, such as the regression and cure which have occurred in a small proportion of cases of choriocarcinoma of accepted authenticity.

Trophoblastic invasion of the uterine wall and of the decidua is seen in both normal pregnancy and with benign hydatidiform mole, though it varies greatly in degree. The histologic pictures thus produced have been very frequently misinterpreted as choriocarcinoma. Such errors are so common that they have greatly vitiated the statistics of choriocarcinoma, which is not nearly so common as some reports have indicated, and which is far more malignant than would appear from the reports of material which unquestionably included many benign choriomatous lesions. It seems scarcely necessary to add that the microscope, and not the biological test, is the arbiter of diagnosis.

Trophoblastic proliferation is a constant feature of even the most clinically benign hydatidiform mole as it exists in situ, the examination of extruded or curetted material being unreliable as giving a true picture in this respect. However, in the presence of a well-preserved villous pattern, almost regardless of the amount of trophoblastic overgrowth, one is not justified in making the diagnosis of choriocarcinoma.

Where trophoblastic proliferation is excessive, or where there is a marked intravascular penetrative tendency, the diagnosis of penetrative, invasive, or destructive mole, or chorioadenoma destruens, may be justified if one wishes to indicate an intermediate group. However, the morphologic characteristics in this group often differ in no noteworthy respect from those of the benign group.

Moles of this type do not metastasize, though they may occasionally invade the vagina or the parametrium, and they can ordinarily be cured by hysterectomy, so that they should not be placed in the malignant group.

The scheme of classification suggested by Hertig and Sheldon as a guide to therapy, and based on the examination of extruded or curetted material is an undesirable one for reasons discussed in this paper. It is to be feared that it may lead to many unnecessary hysterectomies.

Far more important than such histological nuances as those described by Hertig and Sheldon are certain clinical features presented by these lesions. If, after thorough evacuation of a mole, the biological test remains positive or perhaps increases, with sometimes persistence of bleeding, and often a persisting subinvolution of the uterus, hysterectomy is fully justified. In most such cases the examination of the removed mole will show residual molar tissue deep in the uterine wall, beyond the reach of the curette, and not choriocarcinoma. However, in a minority of cases, not determinable by any other method than hysterectomy, genuine choriocarcinoma will be revealed. It is this consideration which fully justifies the operation, as well as the fact that such residual trophoblastic tissue can later give rise to choriocarcinoma.

An interesting fact not always thought of is that choriocarcinoma is not a tumor of the uterus, but of the embryonic trophoblast. Unlike other types of cancer, in which both the invading and the invaded tissue belong to the same individual, a choriocarcinoma represents a tumor of one individual growing in and invading the tissues of another. This may have some importance in the interpretation of such choriomatous tumors, although I can make no suggestion as to what it is.

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Discussion

DR. BAYARD CARTER, Durham, N. C.—In his opening paragraph Dr. Novak stresses that many specimens of hydatidiform mole and of choriocarcinoma were not included in this review of 70 moles and 30 choriocarcinomas, because of the poor material and insufficient clinical data. He shows clearly that the purely clinical features of these two chorionic diseases are directly dependent upon their pathologic characteristics. The precaution must be observed of making this pathology include the living, biological characteristics of both fetal and maternal tissues.

He restates the knowledge that, in most of the ordinary forms of epithelial neoplasms, the histologic features may be relied upon to determine whether the neoplasm under consideration is benign or malignant. However, in lesions of the trophoblast, a tissue which is normally invasive, the factor of the resistence of the maternal tissues to these invading elements may vary greatly. Therefore, in studies of mole and choriocarcinoma, simple morphologic considerations are of far less importance than in other pathology problems.

Classifications have been founded upon the structural and quantitative characteristics of the trophoblast with no true regard for the defense mechanism of the maternal tissues or of maternal systemic functions. Little is known of the nature of any maternal defense mechanism. Is there a systemic antitrophoblastic defense mechanism and, if so, of what nature is it? Unfortunately, there is at present no answer to this question.

The degree of trophoblastic-cell invasion is quite variable and this invasion is frequently marked in the implantation area. This normal invasion at the site is often mistaken for choriocarcinoma.

The author's concept of normal trophoblastic invasion of the uterine tissues is that in this normal invasion the cells, *singly*, infiltrate along the tissue spaces and cause no lytic or destructive reaction in the uterine musculature. In choriocarcinoma, however, large masses or columns of trophoblastic cells infiltrate the uterine musculature, destroy it, and the tissues show the resultant coagulation necrosis and hemorrhage.

Dr. Novak again points out that even in normal pregnancy trophoblastic tissues do penetrate the blood vessels and the same feature is found in study of clinically benign moles. When the vascular penetrability is increased, moles have been designated as "destructive moles," "malignant moles," or "chorioadenoma destruens."

From careful scrutiny of our own material and of the material which came through the Registry, we concur with Dr. Novak's opinion that the difference between a malignant mole and a benign mole is found not only in the more marked proliferation of the trophoblast but also in the abnormally great intravascular invasion, even though the cellular characteristics may be, and often are, identical.

Dr. Novak suggests for the intermediate group of moles the term "penetrative" or "destructive" moles. This group, in his experience, does not cause distant metastases and may be cured by hysterectomy.

He emphasizes that the study of extruded or curetted molar tissues shows a great difference between these tissues and tissue obtained with the mole in situ.

As I understand the thesis, one of his guiding principles is that, when the villous pattern shows a sharply demarcated margin between the stroma and the trophoblast, a mere excess of trophoblast, no matter how pronounced, does not justify a diagnosis of choriocarcinoma.

Dr. Novak expresses the fear that the pathologic classification of Hertig and Sheldon, as a guide for therapy, is undesirable and might lead to the performance of many unnecessary hysterectomies. We have found the classification of Hertig and Sheldon very useful and stimulating. We, however, subscribe to Dr. Novak's thought that therapy had to rely on certain clinical features of the lesions rather than on a histologic picture.

For us it has been a stimulating experience to have passed through our laboratory much of the pathology material from the Registry upon which the author has conducted a part of his erudite study. We would like to express our indebtedness to Dr. Holman for his appreciation of the true necessity for this Registry.

From review of these tissues and from a careful reading of Dr. Novak's paper, we will continue to feel justified in maintaining our conservative attitude in the clinical management of patients with hydatidiform moles.

DR. ELEANOR DELFS, Baltimore, Md.—As Dr. Novak has mentioned, we have had an opportunity in the past five or six years to make a study of 41 hydatidiform moles and 5 chorionepitheliomas with repeated quantitative serum assays for chorionic gonadotropin. The 41 moles varied in the amount of trophoblastic proliferation and cellular changes seen and all degrees of pathological trophoblast were represented. Repeated quantitative serum assays were carried out, and though all were strongly positive at the start, 31 or 75 per cent of the 41 cases were negative by the sixtieth day following expulsion of the mole. An additional 5 cases continued to decrease and ultimately became negative. Thus, approximately 88 per cent of the mole cases proved to be benign and it was possible to treat them conservatively with the feeling that we were not doing an injustice by omitting hysterectomy. The remaining 5 cases had persistently positive assays or rising titers.

One of these patients had a continuing low gonadotropin level without rising titer and on hysterectomy was found to have only a little trophoblast which was probably dying and certainly was not malignant. In retrospect, this patient might have been spared the hysterectomy. Three of the cases showed growth of trophoblast deep in the myometrium, two being of the malignant mole or chorioadenoma destruens type and the other being chorionepithelioma. In these cases the biological assay indicated that actively growing tissue was present. The fifth patient had persistent serum gonadotropin with a slowly rising titer. Hysterectomy was done and serial section of the uterus showed nothing. The chorionic gonadotropin is still positive and I feel sure that this patient has growing trophoblast probably of the malignant type somewhere though physical and x-ray examinations are negative.

Of the five cases of chorionepithelioma we have studied, four were far advanced with generalized metastases when first seen and the biological assay was merely confirmatory. The other was probably one of primary chorionepithelioma, the diagnosis being made on curettings from a very early incomplete abortion. Three weeks elapsed before this patient got back into the hospital and a single biological assay (at a level designed to detect 400 units or more) was negative. Repeat assay three days later was positive at 950 I.U. per liter. On that day the patient had a total hysterectomy and in the uterus was one area a few millimeters in diameter with typical choriocarcinoma cells. This brings up the question of equivocal tests reported in the literature in which alternating positive and negative results have been reported for the same case. Evidence at present indicates that chorionic gonadotropin is produced by the cytotrophoblast and if there are enough of these cells producing it, tests will be positive. If there are very few cells they may not produce enough to affect the test animal—it is a quantitative matter. We have had no tests which clearly contradict that to the present time.

DR. JAMES K. QUIGLEY, Rocheser, N. Y.—Inasmuch as Dr. Novak mentioned the danger from the invasion of the uterine wall, and from hemorrhage, I would like to call attention to the possible danger of severe toxemia associated with hydatid mole. I have seen three such cases. One case was so severe that the patient almost died before delivery of the mole. I did not have permission to empty the uterus until she became desperately ill with high temperature, extreme degree of jaundice, severe anemia, and was in an oxygen tent in extremis. The improvement following emptying of the uterus was miraculous for in less than twelve hours she was almost a well woman. Another point of interest in this particular case was that she developed a luteinizing cyst which did not regress but went on to grow to the size of a baby's head. The cyst required removal two months after the uterus was emptied.

DR. RICHARD PADDOCK, St. Louis, Mo.—As an accessory pathological phase in hydatid mole and chorionepithelioma there should be mentioned the multiple lutein cystomas of the ovaries, that are so frequently associated with these tumors. These tumors are usually spoken of as luteincystoma or lutein cysts, but I believe that they come from the theca lutein cells and not from the true lutein cells. There is much confusion in the terminology. They probably represent the effect of unusual proliferation of placental elements and they require no surgery. They may represent a defense mechanism on the part of the body or ovaries to counteract the effects of growth of these placental elements which are so rapidly proliferative.

GENITAL CANCER AMONG WOMEN*

Factors Affecting Its Control in an Urban Population

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THIS study summarizes the treatment of 1,607 women with one or more types of genital malignancy cared for in Dallas, Texas. Included were patients with cervical carcinoma seen during the ten year period, 1936-1946, and women with some other type of genital cancer seen during the eleven year period, 1936-1947. Three important findings are discussed: (1) frequency of occurrence among women less than 30 years old; (2) relation of the delay between onset of symptoms and diagnosis of the various types of genital tumor; (3) analysis of mismanagement, by physicians, of patients with genital cancer. It was apparent that the average practitioner saw so few women with genital cancer he was not impressed with the magnitude of the public health nature of the problem.

The report is presented with the opinion that women with genital cancer were treated as well in Dallas as in any city of similar size. Therefore, it is suggested that measures to improve upon the care of this kind of patient in Dallas might be applicable to other communities.

Procedure

The project was begun in March, 1946, and completed in December, 1948. Records in the record libraries and pathology departments of all the hospitals and three of the private clinics in Dallas were reviewed. Cancer death certificates in the Bureau of Vital Statistics of the City of Dallas and the County Clerk's Office of Dallas County were analyzed. The American Cancer Society, Texas Division, Inc., granted funds to employ clerical help and to purchase key sort cards for the recording of data collected. Over 80 per cent of the patients were traced by a questionnaire sent to the patient's family, or physician, or to both.

One thousand eight hundred four women had a clinical diagnosis of genital cancer. One thousand six hundred seven of them with histologic diagnoses were studied. Twenty women with feminizing ovarian tumors were not included because it was usually impossible to ascertain by histologic examination whether or not these neoplasms were malignant or benign. The different types of cancer are given in Table I. The distribution compares favorably with Miller's figure for the University of Michigan.[23]

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TABLE I. TYPE OF CANCER

CANCER	NUMBER
Cervical carcinoma	992
Ovarian cancer	294
Endometrial carcinoma	227
Uterine sarcoma	36
Vulval cancer	34
Vaginal cancer	13
Urethral cancer	6
Chorionepithelioma	4
Carcinoma Fallopian tube	1
Total	1,607

Age of Patient

Cancer is usually considered to be a disease of old people. Statistically that is true, but Table II indicates that genital cancer is not uncommon in young women. Note, only 0.4 per cent of those with endomentrial carcinoma were under 30 years old as contrasted to 4.0 per cent with ovarian cancer, 5.0 per cent with cervical, 8.4 per cent with vaginal, and 8.6 per cent with vulval cancer. Ostensibly, corpus carcinoma occurs infrequently before the age of 30 while cancer of the vulva is more common under this age than standard textbooks indicate.

TABLE II. AGE OF PATIENT

	PATIENTS		
		UNDER 30 YEARS*	
CANCER	NUMBER	NO.	PER CENT
Cervical carcinoma	992	49	5.0
Ovarian cancer	275	12	4.0
Endometrial carcinoma	221	1	0.4

*There were six other cancer patients under 30 years of age. Three of them had vulval cancer, and one each uterine sarcoma, vaginal cancer, and chorionepithelioma.

Symptoms

Table III shows the average delay between the onset of first symptoms and the time a correct diagnosis was made. Observe that the average time wasted exceeded six months for all except carcinoma of the urethra. Probably dysuria, a usual symptom of this disease, caused these patients to seek treatment relatively early. Those with uterine sarcoma wasted the most time. Delay for all types of cancer was about the same in 1936 and 1946. Indigent and private patients referred into Dallas for care lost more time than did private patients seen originally in Dallas. This waste was probably due to time required, respectively, to establish the status of indigency and to arrange an appointment in Dallas.

TABLE III. DURATION OF SYMPTOMS

CANCER	AVERAGE DELAY IN MONTHS
Uterine sarcoma	12.8
Vulval cancer	11.7
Endometrial carcinoma	10.5
Vaginal cancer	10.2
Ovarian cancer	8.5
Cervical carcinoma	7.4
Chorionepithelioma	7.0
Carcinoma Fallopian tube	6.5
Urethral cancer	3.3

Pathology

The histologic grade and type were usually given for all the genital tumors except ovarian neoplasms. The variety was unspecified for almost half of these. The diagnosis of chorionepithelioma fell into two categories. In one, the clinical and histologic findings supported the diagnosis of cancer. In the other there was difficulty interpreting the microscopic findings. Since patients with the equivocal diagnosis survived, the question arises, did they have cancer? It is worth noting that one patient with urethral cancer had an adenocarcinoma. Prior to 1947 less than 40 adenocarcinomas of the female urethra were reported.[3, 11, 42]

Descriptions of the pelvic findings were so terse for more than half of the patients with cervical, endometrial, ovarian, and vulval cancers that the tumors could not be classified clinically. Attempts to classify these tumors were seldom done except by physicians devoting a great share of their time to the treatment of cancer. Often these clinicians received the woman after she had been treated by a less experienced person and the clinical grade of the tumor undetermined initially.

One out of every 107 women had more than one primary cancer. Multiple primary malignant lesions tended to involve the organs of closely related systems. This was the observation of Hurt and Broders.[16]

Treatment

Treatment for genital cancer was frequently unstandardized. Nearly one-sixth of the women with cervical carcinoma received improper surgical treatment. One in fifteen women was purposely treated by simple hysterectomy while another one in ten was treated either by this measure or a less formidable procedure for a supposedly benign disease.

Apparently endometrial carcinoma was often unsuspected because subtotal hysterectomy was performed in 25 per cent of the cases. No record of an antecedent diagnostic curettage was given for one-third of the patients. Even after a correct preoperative diagnosis was made, irradiation and operative treatment were not always coordinated properly. Using six weeks or less as a correct interval, proper coordination of irradiation with total hysterectomy and bilateral salpingo-oophorectomy was made for only one woman in ten.

Sarcoma of the uterus was usually an incidental finding to operation for fibroids. The ratio of patients treated by subtotal hysterectomy and total hysterectomy was 2 to 1.

Only one in 42 women with ovarian cancer was known to have a total hysterectomy and bilateral salpingo-oophorectomy. Occasionally part of the omentum was resected. All other women had either irradiation to the pelvis or less adequate operations. Even after removing an ovarian tumor that proved to be malignant histologically, seldom was a second laparotomy done to remove the other adnexa and uterus until a recurrence appeared. The tumor was spilled or tapped among one in nine women.

More than half of the patients with vulval cancer had operable tumors but resection of the regional lymph nodes was seldom done and then only partially. The procedure was never used for urethral cancer and malignant neoplasms of the lower third of the vagina.

Surgical treatment for chorionepithelioma and carcinoma of the Fallopian tube appeared to be standardized.

Irradiation was usually employed in proper amount. The principal difficulty was that the radiotherapist was called in consultation often to administer palliative treatment after improper surgical measures had been administered.

Supportive treatment, particularly for anemia, was frequently neglected among patients irradiated. Undoubtedly this sometimes precluded satisfactory tolerance to, and recovery from, irradiation.

Results

There were too few patients with any one type or grade of tumor treated by any one method to evaluate treatment properly. On the other hand, it was possible to ascertain that survival rates among those treated with conventional methods were better than among those receiving poorly coordinated or improper treatment. Patients with cervical carcinoma subjected to subtotal and total hysterectomy more commonly had distant metastases and vaginal hemorrhages than did those not operated upon. Survival rates among women with corpus carcinoma treated by preoperative radium intracavitary and total hysterectomy and bilateral salpingo-oophorectomy were better than among those treated by either irradiation or operation alone. Those with uterine sarcoma treated by subtotal hysterectomy generally died while those totally hysterectomized ordinarily survived. It was unusual that one woman with chorionepithelioma lived six years after being treated by hysterectomy and irradiation before dying of brain metastases.

Five-year survival rates for the various tumors are compared with collected statistics (Table IV). It is important to know that many of the collected reports contained unstandardized treatments. If all patients had received proper therapy the best survival rates would have been even better.

TABLE IV. SURVIVAL RATES

CANCER	FIVE YEAR SURVIVAL RATES IN PER CENT	
	DALLAS	COLLECTED STATISTICS*
1936-1940.—		
Cervical carcinoma	32.2	20.0-58.1[10, 23, 26, 32, 41]
1936-1941.—		
Endometrial carcinoma	46.5	35.9-85.0[12, 13, 20, 33, 40]
Uterine sarcoma	35.7	17.6-30.8[30, 34, 37]
Vulval cancer	33.3	13.9-42.0[6, 21, 28, 31, 36, 39]
Ovarian cancer	21.3	12.3-45.4[17, 22, 25, 29]
Vaginal cancer	20.0	12.0-17.0[35, 38]
Chorionepithelioma	0.0	34.0-66.0[2, 14]
Urethral cancer†	0.0	
Carcinoma Fallopian tube‡	0.0	

*Superior figures are references.

†There are about 330 women with urethral cancer reported. Few of these survived five years.[3, 6, 9, 11, 38, 42]

‡Less than 500 patients with carcinoma of the tube are reported. Survival rates are available for only a small number of these. Among the combined total of 30 patients recently studied [5,18] 12 women were living, only four more than 5 years.

Comment

This study revealed three things of importance. First, genital cancer was not uncommon under the age of 30 years. Second, there was much time wasted after onset of symptoms before a diagnosis was made. A great deal of the delay was attributed to the patient. Miller[24] is of the opinion that some patients do not consult physicians for physical examinations because they are embarrassed and discouraged by the indifference or by the inefficiency manifested by some physicians in making examinations. Contrariwise, Edward Allen[1] believes the average woman dislikes a pelvic study. He has suggested that the girl be educated in childhood to request a pelvic study periodically.

Third, and most important, physicians were often guilty of prescribing incorrect treatment or not using proper diagnostic methods. They often fell into the trap of underestimating their opponent while attempting to spare their patients a formidable surgical experience. This mistake was probably often due to a lack of understanding regarding the pathology of the disease. Until it is recognized that the eradication of cancer necessitates the radical approach, results are not likely to improve. This is to say, when surgical measures are used, the immediate routes of spread of the tumor must be removed by block dissection with the primary malignancy. Selection of the type of operation varies with the location and the type of tumor. It is essential that the surgeon evaluate the operability of the tumor before subjecting his patient to surgical attack. Failure to make this evaluation leads to needless or meddlesome operations and an increase in the incidence of various complications.[7] Subtotal hysterectomy has no place in the treatment of uterine cancer and seldom a place even in the treatment of benign uterine disease. Since ovarian and tubal metastases may occur in endometrial carcinoma,[19, 24] tubal and uterine metastases in ovarian cancer,[7, 19, 24] and ovarian and uterine metastases in carcinoma of the tube,[5, 18] the necessity for total hysterectomy and bilateral salpingo-oophorectomy in these diseases is obvious. In addition, removal of the omentum for ovarian cancer has been recommended.[29] To the contrary, its excision is questioned for the reason that distant metastases have occurred elsewhere by the time there is spread to the omentum.[4] Total hysterectomy and bilateral salpingo-oophorectomy have been recommended for treatment of chorionepithelioma of the uterus[2] but recent studies indicate total hysterectomy is sufficient.[14] If distant metastases are present, the prognosis for the patient is probably not changed by removing the adnexa unless they are involved. The writer has the same opinion in the case of uterine sarcoma. On the other hand, Schmitz[34] has recommended the Wertheim operation for this disease. Since it, like chorionepithelioma, usually spreads by the blood stream, the value of the radical procedure for the two diseases will have to await further study. In contrast, all the other genital tumors seldom metastasize by the blood stream but instead by the lymphatics or direct extension. Since cervical carcinoma often spreads early to the regional lymph nodes, they must be excised with the uterus and upper third of the vagina. Total vulvectomy with dissection of the femoral and iliac lymph nodes is to be done for vulval cancer,[21, 28, 36, 38, 39] cancer of the lower third of the vagina,[35] and malignant neoplasms of the urethra.[38]

In some instances irradiation is the procedure of choice and in others a combination of irradiation and operation is preferred to treat certain genital cancers. Radiation is generally preferred to treat invasive cervical carcinoma.[10, 23] In selected cases, radical operation is employed.[32, 41] Since discouraging results continue to be obtained with irradiation or surgery alone, a combination of the two measures has been suggested.[26] Preoperative irradiation given a few weeks before total hysterectomy and bilateral salpingo-oophorectomy ostensibly improves results for carcinoma of the fundus.[12, 13, 27, 33] The neoplastic cells are damaged by radiation so that they are unlikely to survive in the operative field. Waiting longer than 6 weeks after radium treatment to do the operation allows regeneration and spread of the undestroyed cancer cells.

The value of irradiation in the treatment of ovarian cancer, uterine sarcoma, chorionepithelioma, and carcinoma of the tube is difficult to judge. It probably cuts down ascites formation and slows the growth[7, 17, 25] of implants or recurrences but, as far as effecting a cure, that remains equivocal.

The use of x-rays and radium is not the treatment of choice for operable vulval cancer.[21, 28] Their use for cancer of the lower one-third of the vagina and urethral cancer[6] should be combined with operation. Irradiation is the principal measure used to treat cancer of the upper two-thirds of the vagina.[35]

This study indicates that it would be advisable to establish tumor committes universally to educate the physician, be he specialist or general practitioner, on a plan similar to the one used in Philadelphia.[15] Women, particularly those past middle age, should be encouraged to have a pelvic study periodically. When abnormal genital symptoms are given by patients, their cause should be established by using appropriate diagnostic procedures, including, if necessary, biopsy, uterine curettage, and cytologic methods. The latter may be valuable in detecting the early cancers unrecognizable clinically. It is essential that physicians treating women understand the pathology of genital cancer and its proper treatment.

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Discussion

DR. A. N. CREADICK, Rocky Hill, Conn.—The greater value of this paper may not be intrinsic but rather rests on its use as a basis for comparison with subsequent quinquennial studies to measure progress in the care and treatment of similar cases in the area. In all probability conditions demonstrated in Dallas were not dissimilar from those of other areas before the recent more intensive attack on cancer was undertaken.

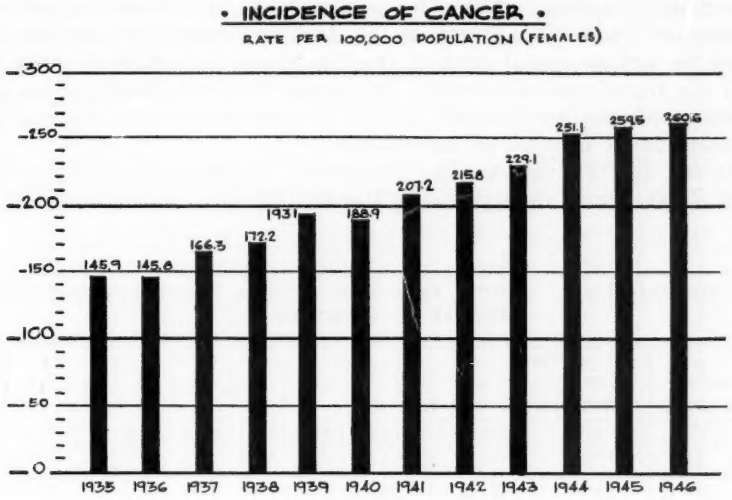

Fig. 1.

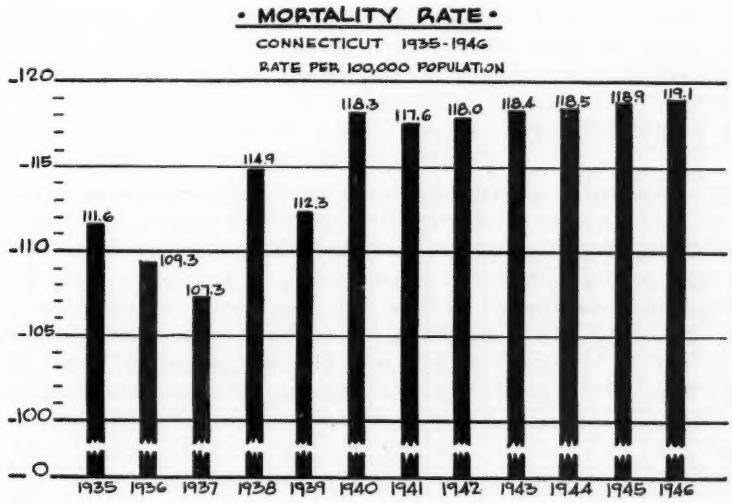

Fig. 2.

It is one thing to analyze the results in one operator's hands, or in a clinic where uniform standards of diagnosis, methods of treatment, operative skills, and modern pre- and postoperative care are used. It is entirely different to review the statistics of a community where a dozen groups and thirty individuals are working and where the neglected or unwilling cases are all too numerous. No one operator nor one clinic can care for a large enough sample to be significant. Studies such as the one at present under discussion must be made before continued support or criticism of the nation-wide propaganda can be justified.

I would have preferred that the Dallas figures be presented in quinquennial periods for it is well understood that the clinical attack on this disease undergoes periodic change with preference for one or another approach and with improvements in technique.

Emphasizing my points and corroborating Dr. Diddle's, I call your attention to the Connecticut figures. We began our campaign in 1933; our registry of cancer cases began in 1935. The General Assembly gave a grant-in-aid to establish clinics. We instituted a drive to alert the practitioner. We established tumor clinics in 1938. The Division of Cancer Research in the State Department of Health was organized. We formed an association with the national group of Dr. Little's known as the American Association for the Control of Cancer. In 1944 the first successful drive of the Connecticut Cancer Society was conducted. We began with the registry of all cases in the general hospitals diagnosed as cancer and then all the death certificates were checked. Finally we succeeded in securing nearly complete registration. Gradually we included all known cases.

The charts and figures I present were prepared by the Statistician of the Division of Cancer Research of the State Department of Health. Each chart and table tells its own story.

TABLE I. SURVIVAL RATE. CANCER, CORPUS OF UTERUS, MICROSCOPICALLY PROVED, FOLLOW-UP COMPLETE

YEAR OF ADMISSION	TOTAL TREATED	% ALIVE YEAR OF TREATMENT	1 YR.	2 YR.	3 YR.	4 YR.	5 YR.	6 YR.	7 YR.	8 YR.	9 YR.	10 YR.	11 YR.
1935	70	80.0	60.0	54.3	48.6	41.4	37.1	34.3	31.4	28.6	28.6	27.1	27.1
1936	64	79.7	54.7	48.4	43.8	37.5	32.8	31.3	28.1	28.1	26.6	25.0	
1937	76	80.3	60.5	51.3	44.7	43.4	40.8	39.5	32.9	26.3	25.0		
1938	79	79.7	69.6	57.0	45.6	45.6	41.8	40.5	36.7	35.4			
1939	98	80.6	69.4	56.1	51.0	48.0	42.9	41.8	39.8				
1940	114	78.1	64.0	58.8	53.5	48.2	43.9	42.1					
1941	106	88.7	78.3	72.6	67.0	61.3	61.3						
1942	118	89.0	76.3	66.9	63.6	61.9							
1943	118	83.9	73.7	64.4	58.5								
1944	157	89.8	74.5	66.9									
1945	145	93.1	81.4										

TABLE II. SURVIVAL RATE. CANCER, CERVIX OF UTERUS, MICROSCOPICALLY PROVED, FOLLOW-UP COMPLETE

YEAR OF ADMISSION	TOTAL TREATED	% ALIVE YEAR OF TREATMENT	1 YR.	2 YR.	3 YR.	4 YR.	5 YR.	6 YR.	7 YR.	8 YR.	9 YR.	10 YR.	11 YR.
1935	130	88.5	62.3	46.9	40.8	35.4	33.1	30.8	27.7	26.9	25.4	23.8	23.1
1936	149	79.2	52.3	43.0	39.6	34.9	32.9	29.5	27.5	26.8	25.5	25.5	
1937	161	80.7	50.3	37.9	30.4	29.2	26.7	25.5	25.5	24.2	24.2		
1938	145	83.4	57.2	42.1	34.5	32.4	31.0	26.9	24.1	24.1			
1939	155	83.2	56.8	42.6	39.4	34.2	32.9	30.3	29.0				
1940	136	81.6	55.1	48.5	45.6	41.2	39.0	38.2					
1941	180	81.1	62.2	53.9	47.8	42.8	40.6						
1942	199	84.9	60.8	50.3	46.7	44.2							
1943	195	84.1	60.0	52.3	46.7								
1944	211	86.7	64.9	55.9									
1945	203	85.2	69.5										

As time went on, surgical training improved, x-ray and radium therapy improved, preoperative and postoperative care, including more frequent use of antibiotics, transfusion, etc., produced a remarkable first-year salvage which is reflected in a modest improvement in

the five- and ten-year survivals. The continuing record of the Dallas area with Dr. Diddle's paper as a start will contribute like information.

One or two points of criticism of the intrinsic content of Dr. Diddle's paper should be mentioned: The first is the unusually high incidence of carcinoma of the external genitals. I am convinced that the figures collected in Dallas represent in the case of ovarian, uterine, and tubal malignancy the ordinary proportion of such cases in that metropolitan area, whereas malignancy of the external genitals is not incapacitating, is apparent, and probably represents a number of cases from a wider geographic area because of ease of transportation. It is not likely that his figure represented an unusual susceptibility of the population of Dallas to that particular form of cancer.

TABLE III. PERCENTAGE DISTRIBUTION, CANCER BY AGE, MICROSCOPICALLY PROVED, WOMEN

	0-9 YEARS	10-19 YEARS	20-29 YEARS	30-39 YEARS	40-49 YEARS	50-59 YEARS	60-69 YEARS	70-79 YEARS	80+ YEARS
Corpus of uterus	–	.2	2.1	4.8	18.1	32.1	28.7	11.4	1.9
Cervix of uterus	–	.1	2.3	14.1	29.7	29.1	17.0	6.2	.7
Ovaries	–	1.6	4.8	10.3	24.3	30.5	20.5	6.3	1.1
Fallopian tubes	–	–	–	–	13.3	66.7	13.3	6.7	–
Vagina	–	1.3	1.3	5.2	20.7	22.1	22.1	18.2	9.1
Labia Minora and clitoris	–	–	–	3.1	6.3	12.5	40.6	31.2	6.3
Total	–	.5	2.7	10.3	24.7	30.2	21.5	8.1	1.3

The high incidence of chorionepithelioma, I suspect, depends on poor pathological diagnosis. It is extremely difficult at times to make the correct diagnosis.

DR. HOWARD C. STEARNS, Portland, Ore.—Portland, Oregon, is like Dallas, Texas, in regard to cancer, both from a professional and lay point of view. It has been a struggle in our community over many years to get surgeons to yield to x-ray and radium their present positions in the treatment of cervical carcinoma. It has been necessary to press strongly for irradiation of known corpus carcinoma prior to surgical extirpation and to emphasize that vulvectomy is not enough in cases of vulvar carcinoma.

Dr. Diddle's study certainly points out weak spots in management of the genital-carcinoma problem. It suggests that our goal, in addition to research, must be to stress two important factors. First, to keep all physicians thoroughly abreast of methods of cancer detection and therapy, and, second, to educate women to recognize common signs and symptoms of genital cancer. While we have a long way to go in the matter of early recognition and adequate therapy of cancer, proper use by the profession of the knowledge we now possess would do much toward improving control. I am glad to report that in the Pacific Northwest we do have an alert and cooperative profession so far as cancer educational work is concerned and I suspect that this is true the nation over.

Our experience in regard to patient negligence parallels that found in Dallas. In 228 consecutive cases of cervical carcinoma seen at the University of Oregon Medical School clinics, only 16 per cent sought medical help within 30 days after symptoms were first noted; 24 per cent presented themselves between one and three months after onset of symptoms, 18 per cent between three and six months, 18 per cent between six and twelve months, and 24 per cent after more than one year. Our charity patients in the teaching clinics present themselves for treatment later than our private patients and it is not because they lose time in qualifying for free care. It is my impression, based on many years of work with this charity group, that ignorance and indolence are the factors which cause the delay. If this is true, our present administration's contention that making medical services readily available "without cost [sic]" would correct the evils of such delay is not tenable. There is nothing more readily available to our poor without cost (to them) than our medical school clinics.

Of 358 consecutive cases of cervical carcinoma seen at the University of Oregon Medical School from 1930 to 1949, 65 were placed as Stage I, 58 as Stage II, 91 as Stage III, and 144 as Stage IV. Forty-six of the 64 Stage I group still live, while only 37 of the 58 stage II, 38 of the 91 Stage III, and 9 of the 144 Stage IV group remain alive. Four persons each of the Stages I and II are known to have persistent cancer, while 10 of the Stage III group and 7 of the Stage IV are still affected and will die of cancer.

The moral here, as well as in the Dallas study, is plain—teach the woman to seek help early and as a medical group let us see that such help is competent.

I agree with Dr. Diddle on his concepts of therapy. Surgery in cervical carcinoma will be more useful when we learn by one means or another which growths may be vulnerable to irradiation and which not. Studies to this end must be pressed. Cytological studies, in addition to their value in early diagnosis, show promise in this regard.

DR. FREDERICK S. WETHERELL, Syracuse, N. Y.—It is easy for us as specialists to criticize the general practitioner and the near-specialist for missing early diagnosis, for not studying his cases well enough to detect cancer early.

The cost of a detection clinic is high. Thousands of dollars are being poured into these detection clinics; too few cases of malignancy are found for the money expended. I am trying to impress upon you the importance of making every physician's office a detection clinic. Why not have a little slip of paper with the eight or nine questions leading to cancer suspicion, in the office, which the patient while waiting could check "Yes" or "No"? A rough screening method, but nevertheless one which would keep us alert.

DR. HERBERT E. SCHMITZ, Chicago, Ill.—The essayist's paper is of great value and will stimulate all of us to return home and attempt to detect carcinoma in its early stages. I am not as concerned with the detection of the disease in recent years, as I am with its treatment. After it has been detected, is it treated properly? We are seeing more and more patients referred into the tumor clinics who have been subjected to inadequate and incomplete therapy, and I wonder if this is not due to the fact that we are not accepting our responsibility of teaching, not only the general practitioner who always receives the brunt of our criticism, but the so-called fellow specialist. For example, in one of our large charity hospitals in Chicago we have the opportunity in the tumor clinic of reviewing the work of eight gynecologic specialists, well-accepted, well-trained teachers. You would be surprised if I were to tell you the total results of the treatment chosen by these eight different men and their associates. Let us not pay too much attention to the general practitioner. I am quite sure that we can readily teach him to detect the disease and, in most instances, we can teach him to cooperate with us in referring his patients to properly equipped institutions, but let us give attention to the staffs of these institutions who are going to treat the disease. Let us begin to clean our own house. I think that is a very important matter.

DR. DIDDLE (Closing).—In answer to Dr. Creadick's point about the chorionepithelioma, it was brought out in the paper that probably all the patients who got well did not have chorionepithelioma. The young patients who had vulvar cancer usually had had granuloma inguinale for a number of years.

Dr. Wetherell's comments are well taken. Recently I was asked to serve in the east end of my state on this problem. In this community, physicians too often feel that cancer is a hopeless disease and have too little enthusiasm in its treatment.

This study also emphasizes the fact that patients frequently were not kept in condition to tolerate complete treatment. At the present time it is apparent that our efforts would be better spent by using known methods of treatment properly and considering new techniques of diagnosis as still in the experimental stage.

(The paper by Dr. Willis E. Brown on "A Study of Antidiuretic Effect of the Depressant Drugs Used in Eclampsia" will be included in the July issue of the JOURNAL.*)*

Original Communications

PREGNANCY CHANGES IN THE UTERINE CERVICAL GANGLIA (FRANKENHÄUSER) AS CAUSATIVE FACTORS OF VASCULAR HYPERTENSION IN TOXEMIA

J. HOFBAUER, M.D., CINCINNATI, OHIO

THE motivating thought throughout the recent approach to the physiopathology of hypertension in late toxemia is reflected in the novel conception that it involves a functional derangement of a specific hemodynamic mechanism which normally maintains the dynamic blood pressure equilibrium in the pregnant organism. In the balanced opposition of contrary vasotropic stimuli associated with gestation, the heightened activities of the basophiles of the prepituitary and the adrenal cortex, combined with the unusual responsiveness of the arterioles in regard to the pressor principle of the postpituitary, predispose to hypertension, while placental acetylcholine acts as the potent vasodepressor.[5]

Pursuing further the investigation concerning hitherto unknown factors inherent in the pregnant organization which may be of particular relevance in the pathogenetic mechanism of the hemodynamic abnormality, the present communication purports to highlight the marked secretory activation of the chromaffin elements and their remarkable numerical increase in certain sympathetic ganglia located lateral to the upper wall of the vagina and the uterine cervix. These structures may appear as a cluster of smaller ganglia or may be conglomerate in one discrete and crescent-shaped unit, collectively termed the cervical or cervicouterine ganglion of Frankenhäuser, who first described this sympathetic plexus and observed its enlargement during gestation in the human being. Histologically, large multipolar nerve cells with a rich supply from nonmyelinated nerve fibers constitute the bulk of this structure while smaller polygonal elements with a distinct staining affinity for bichromate and ferrichloride constitute a considerable quantity of the cellular content.[1] Predominantly arranged in groups or nests in the periphery of the ganglion, these chromaffin elements display a close resemblance to the pheochromocytes of the adrenal medulla. Fibers from the lower dorsal and the first and second lumbar sympathetic nerves in the hypogastric plexus enter the cervicouterine ganglion, making synapses with other nerve fibers which extend to the lateral side of the uterus, cervix, and vagina. Abundant twigs of the parasympathetic pelvic nerves also enter the ganglion. Sensory organs resembling Pacini corpuscles represent interesting components. They are

connected with the large nerve trunks from the sympathetic and spinal nerves which supply the cervical ganglia and are considered to function as pressure and strain receptors while some investigators interpret them as regulators of blood pressure. Occupying a position upon the posterior surface of Mackenrodt's ligaments, the arrangement of the cervical ganglia appears to be in relation to the physiological changes of the adjacent organs (Peham).

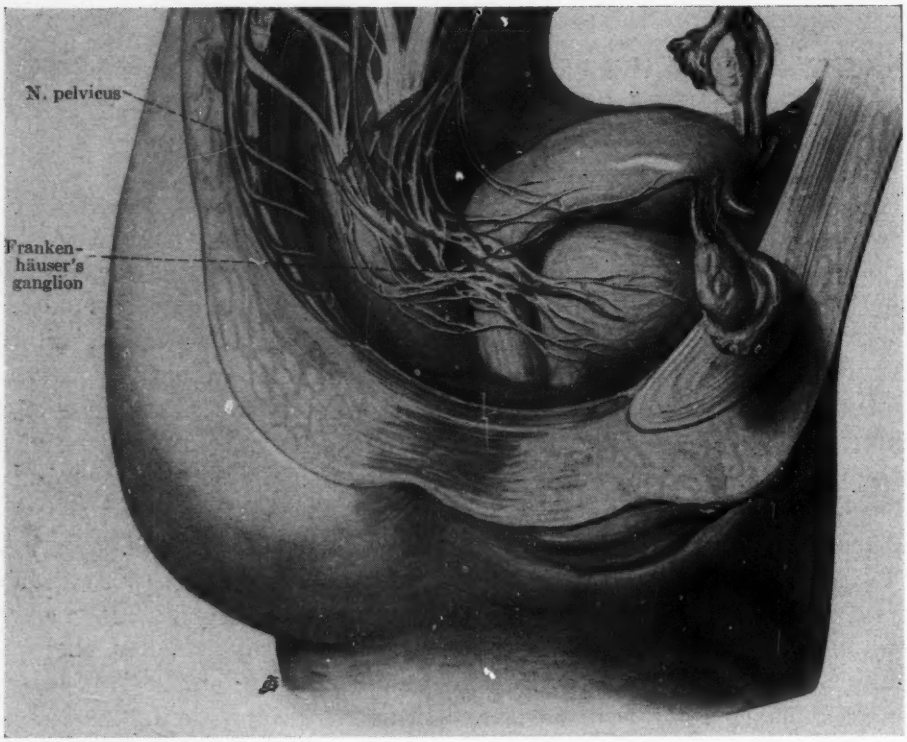

Fig. 1.—Topography of the Frankenhäuser ganglion. (From Peham and Amreich: Operative Gynecology, English edition, Philadelphia, 1940, J. B. Lippincott Company.)

The part played by the cervical ganglia in receiving, coordinating, and conveying to the uterus motor impulses is beyond the province of this paper which aims to accentuate the biological significance of these structures during gestation as *accessory adrenal-medullary* formations and to discuss their interrelation with the adenohypophysis, the adrenals, the ovaries, and the placenta. In our experimental analysis of the hormonal causative mechanism of various gynecologic disorders, the loss of staining capacity of the components of the cervical ganglia was observed subsequent to the removal of the adenohypophysis, or the adrenals, or the ovaries.[6] As a matter of considerable interest, restoration to normal conditions could be effected by the parenteral administration of adrenal extracts and estrogens. The importance of estrogens of ovarian or placental origin and of adrenal extracts as trophic impulses to the effector elements of the cervical ganglia emerged from these observations in laboratory animals. The significance, for the maintenance of the structural integrity of these ganglia, of estrogens was first stressed by the investigations of Kennedy, who observed a rapid decrease of the number of the chromaffin cells and loss of their adrenaline content following castration.[4]

Previous studies in regard to the finer histology of the parametrium and of the pelvic portion of the ureter during gestation and of decidua formation in the cul-de-sac[7] revealed the incidental finding of a remarkable growth of local ganglion cells. In specimens stained with pyridine-silver solution, the presence of a network of dendrites connecting adjacent large nerve cells of the cervical plexus and carrying bulbous endings was clearly seen. Such formations represent the receptor apparatus of sympathetic ganglia. No multiplication of the large ganglion cells was observed. In contrast, a remarkable multiplication of the chromaffin cells, numbering at term five to six times the initial count as the result of their differentiation from indifferent stem cells, as well as their increased staining affinity to bichromate, commanded attention. In fact, the depth of staining of their chromaffin granules exceeds the staining reaction of medullary cells in other organs. Because of the aggregation of these pheochrome cells as solid formations in the periphery

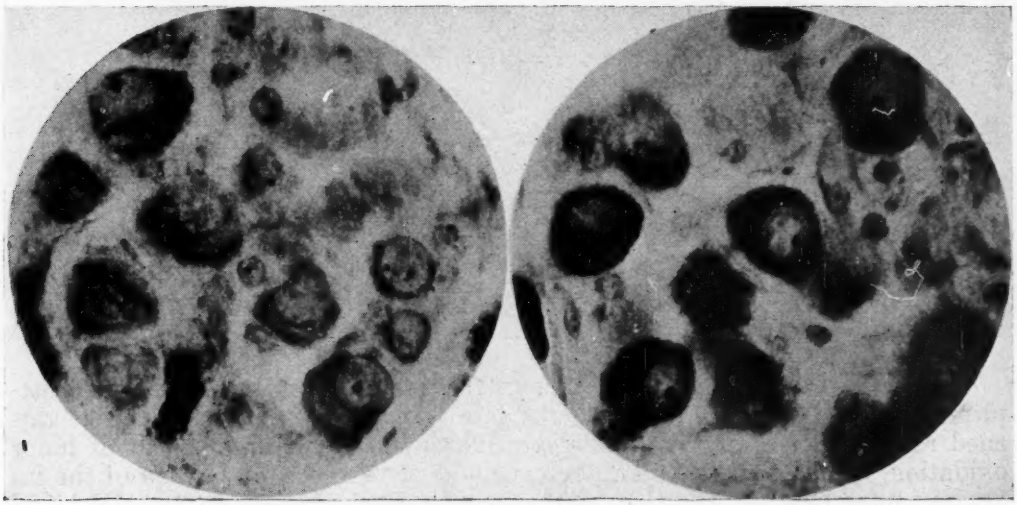

Fig. 2.—Cervical ganglion of castrated mouse (left) and its restitution by exhibition of estrin (right). (After Kennedy, W. P.: Edinburgh M. J., p. 75, May, 1929.)

of the cervical ganglia, they may be designated as chromaffinoma. The histochemical appearance in the pregnant state of these pheochromocytes used as an index of endocrine activity and secretory content points to the increased formation of adrenaline or allied substances, in conformity with the views expressed by Blotevogel,[3] Poll, Kennedy, Penitschka. The significance of the structural metamorphosis of the cervical ganglia incident to gestation, characterized by a distinct enlargement of these nodes and a remarkable activation of their chromaffin elements, emerges from its correlation with the recent recognition of hypermedullary tumors or hyperplastic chromophil tissue as a definite clinical entity (Yater).

To the clear indication of enhanced chromaffin activity and the realization of its stimulating effect on the anterior pituitary-adrenocortical system must be added the consideration of certain mechanical factors. Experimental evidence and clinical observations incident to the removal of pheochromocytoma revealed that slight trauma or massage or stimulation of the sympathetic nerve terminals may cause the liberation and outpouring of adrenaline and noradrenaline from the sensitive chromaffin tissue. As a corollary, due to the increasing intra-abdominal pressure and the enlargement of the lower

uterine segment and the ascent of the uterus from the pelvis into the abdominal cavity in the second half of gestation, the cervical ganglia, situated on the posterior aspect of Mackenrodt's ligament and thus normally sheltered against undue pressure, are exposed to gradually increasing irritation. Pressure from above occurs with the descent of the fetal head, and is intensified when the head enters the pelvis. With the advance of labor, the effect of splanchnic nerve stimulation on the chromaffin tissue incident to uterine contractions provides an additional factor for the liberation of adrenaline. These data may offer a rational basis for the explanation of the higher incidence of toxemia in primiparas, in twin-pregnancy and hydramnios, and for the observation that toxemia occurs only in the second half of gestation, the incidence of eclampsia increasing in proportion to the advance of the pregnant state and reaching its high-water mark during labor. Supporting data for the views expressed may be found in the impressive analogy which exists between the blood findings in toxemia—increased lactic acid and uric acid, hyperglycemia—and the phenomena occurring in adrenalism and hyperfunction of the adrenal cortex.

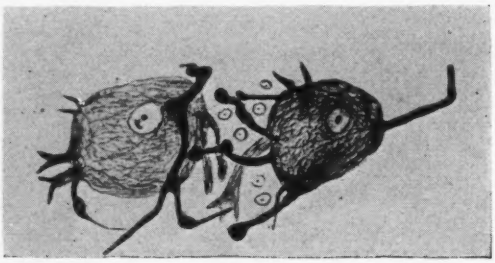

Fig. 3.—Ganglion cells of cervical ganglion at term (silver stain).

An analysis of the pros and cons of the potential role played by the postpituitary gland in the etiology of the late toxemia[5, 8] enumerated the heightened responsiveness of the arterioles to vasopressin, the impairment of inner oxidation, the decrease of alkali reserve and increase in the plasma of the inorganic phosphate, in addition to the increased cohesiveness of the red blood cells (Dodds), as common to both toxemia and experimentally induced hyperpituitarism. In recent years, however, the marked secretory activation of the adenohypophysis during the last trimester of gestation and its distinct augmentation in toxemia were brought into focus. With the remarkable gestational alterations of the cervical ganglia viewed as the result of pituitary and estrogenic impulses, a fuller understanding of the biological factors involved in the mechanism of hypertension as the basic disorder of toxemia is initiated. The intimate association of the prime factors of toxemia with the specific pattern of the pregnant state reserves a place of its own in the broad discussions of the complex problem of the origin of elevated blood pressure, for hypertension in toxemia. The evolution of this new aspect parallels the recognition of specific endocrine stimuli of anterior pituitary and ovarian origin in the development of "pseudomalignant changes" in the endocervix of the pregnant uterus.[8]

The importance of the control exercised by placental acetylcholine over excessive postpituitary effects on the vascular tree was detailed in former publications. Pharmacological evidence points to the activity of the Kupffer cells of the liver, and histaminase, and to oxidation as the principal factors concerned in the inactivation of adrenaline.[8, 15] Impairment in toxemia of these mechanisms[8] entails an imbalance in the homeostatic equilibrium. Considerable interest is currently being displayed in the relation of the adrenal gland to hypertension, and there is much suggestive evidence in favor of the view

that the adrenals have some part and perhaps play a primary and substantial role in the pathogenesis of hypertensive disease.[9] The rich nerve supply from the splanchnic nerves to the chromaffin elements of the adrenal medulla and the experimental evidence showing that minute amounts of epinephrine in the blood effect a sensitization of the vasoconstrictor nerve endings have been invoked as the essential foundation of this relation. Emphasis on hyperplastic changes observed in the zona fasciculata of the adrenal cortex as a frequent concomitant of hypertension calls to mind the consistent occurrence of this phenomenon incident to gestation. With leucocytosis a recognized attribute of labor,[11] the remarkable drop of the blood eosinophile count in toxemia accompanied by increased uric acid blood levels serves to illuminate the activation in this disorder of the *pituitary adrenal-corticotropic hormone* (ACTH).[2]

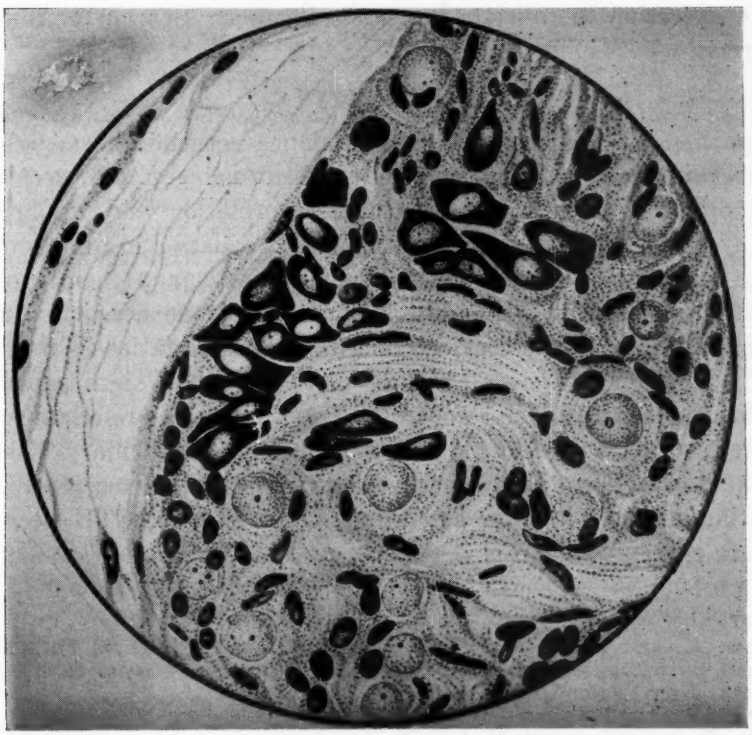

Fig. 4.—Peripheral part of Frankenhäuser ganglion. Note dark-stained chromaffin cells, large ganglion cells, and interspersed between them undifferentiated stem cells. Bichromate fixation (Blotevogel).

The recent demonstration by v. Euler of a specific new sympathomimetic compound in the medullary substance of the adrenal revealed a principle of unexpected importance. As a precursor of adrenaline and differing from it in lacking a methyl-grouping of the amino nitrogen of the molecule, noradrenaline (arterenol) represents a pressor substance liberated from the adrenal medulla on splanchnic stimulation which initiates and maintains sustained arteriolar constriction.[10-15] The amount of adrenaline or noradrenaline in the medullary cells in the human being corresponds to the amount of their pheochrome substance. Extensive research by Bulbring and Burn[10] concerning hemodynamic responses tends to suggest that noradrenaline should be regarded the transmitter of all constrictor impulses and acetylcholine of all dilator impulses. The detection of this new principle in cir-

culation is a matter of extreme delicacy. According to Gaddum[14] one of the main difficulties in the estimation of adrenaline and allied substances in the blood is that various other pharmacologically active substances are formed when blood is removed, and several methods devised for estimating noradrenaline require that only one active substance be present in the solution.

The implication of a multiplicity of pituitary and adrenal principles in the fundamental pathogenesis of the syndrome loosely termed pregnancy toxemia renders illusory in this domain the utilization of recent diagnostic tests for the identification of sympathetic impulses (using benzodioxanes, dibenamine, etc.). Repeated employment of a modified Pissemski method with the perfusion of rabbits' ears supported the view that in the mechanism of vasoconstriction in toxemia adrenaline is involved. The identification of the antidiuretic principle in the excretion in toxemia bears significance. Search for noradrenaline is in progress.

Summary

Recognition of the disturbed delicate balance in certain hormonal regulatory mechanisms and homeostatic adjustments of normal gestation seems to be the nearest visible approach to a coherent interpretation and resolution of the origin of hypertension and impairment of inner oxidation in pregnancy toxemia, and of the laboratory data available. The multifactor approach involves hyperactivity of the pituitary, the adrenal cortex, and the accessory medulla-like formations occurring in the cervical ganglia during gestation as interdependent members of a dynamic system which assumes etiological significance as the result of the inadequacy of its controlling factors. In pre-eclampsia, marked eosinopenia, sodium and chloride retention, increase in urinary 17-ketosteroids and uric acid excretion afford sensitive indicators of anterior pituitary-adrenal cortical stimulation, with the activation of pituitary ACTH secretion most likely due to epinephrine.

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Department of Reviews and Abstracts

Selected Abstracts

Abortion

Campbell, R. G., and Brown, W. W., Jr.: Postabortal Tetanus, South. M. J. 42: 1086, 1949.

Tetanus is a rare but serious sequel to abortion. Until 1941 there had been 170 cases of postabortal tetanus reported. Since that time 14 additional reports have appeared in the literature giving a total of 206 cases with an over-all mortality rate of 76 per cent. The treatment is medical and depends upon massive sedation and antitoxin in huge doses. It is known that the tetanus bacillus is confined to the site of injury and only the toxin disseminates through the body. Following World War II experience there has been a trend toward surgical removal of the infected focus. In the author's case report, hysterectomy was performed and recovery followed. However, it is quite possible that in most patients with postabortal tetanus such a surgical approach may be beyond the physiologic endurance of a very ill patient.

WILLIAM BICKERS.

Anesthesia, Analgesia

Seward, E. H.: Self-Administered Analgesia in Labour, Lancet (London), p. 781, Oct. 29, 1949.

During the early stages of labor small doses of an analgesic drug (Pethidine, chloral, or an opiate) are used. When the cervix is one-half to three-fourths dilated the patient is permitted to inhale anesthetic gases at will. (In the "Warming" apparatus employed, nitrous oxide cannot be inhaled if the oxygen supply fails).

Comparison of anesthetic mixtures in 150 labors showed that 75 per cent nitrous oxide in oxygen, and 0.5 per cent trichlorethylene in air are equally effective in relieving labor pain, and each was markedly superior to 50 per cent nitrous oxide in air, a mixture approved for administration by midwives in England.

In two parallel series of 100 cases, it was found that 75 per cent nitrous oxide in oxygen provided adequate analgesia in 58 per cent, and 0.5 per cent trichlorethylene in air in 91 per cent of patients in labor. Moreover, the latter gas does not produce excitement and hyperactivity. However, it is eliminated rather slowly, and leads to progressive maternal drowsiness and fetal depression if used for periods as long as six hours.

IRVING L. FRANK.

Caldwell, William G.: The Treatment of Postlumbar Puncture Headache With DHE-45 (Dihydroergotamine), West. J. Surg. 58: 11, 1950.

Headache following a spinal anesthesia occurs sufficiently often to limit the clinical usefulness of the procedure. Dihydroergotamine administered as soon as symptoms of headache or vertigo appear has proved to be an effective prophylactic and therapeutic drug. It was administered by the intramuscular or intravenous route with the simul-

taneous injection of caffeine sodium benzoate. This method of treatment has been compared to the conventional therapeutic measures recommended over the last several years and it is the conclusion of this author that the combination of Dihydroergotamine intravenously and caffeine sodium benzoate intramuscularly provides the surest relief of symptoms.

WILLIAM BICKERS.

Endocrinology

Israel, S. Leon, and Schneller, Oscar: The Thermogenic Property of Progesterone, Fertility and Sterility **1**: 53, 1950.

The biphasic character of the basal body temperature in the normally menstruating woman is now accepted. During the follicle stage, the temperature is relatively low. At ovulation there is a rise of about 0.5° F. which continues through the luteal phase until about two days prior to menstruation. If however, pregnancy ensues, the temperature remains at the luteal level.

While the effect of estrogen and progesterone on the temperature curve in amenorrheic women has been studied previously, little work has been done using female castrates. Accordingly twenty-six surgically castrated women were selected for study. Of these, data from fourteen was not used because of lack of patient cooperation. It was found that the administration of ethinyl estradiol in 0.15 mg. doses daily depressed the basal temperature level 0.2 to 0.4° F. If the dose of the estrogen were doubled, no appreciable change in the temperature drop was noted. When 60 mg. of pregneninolone were given daily, the temperature level was elevated in twenty out of thirty times. However, if the dose were increased to 80 mg., the temperature was raised in nineteen out of twenty-two trials. Further experiments showed that the temperature could be slightly depressed by ethinyl estradiol and that when this medication was stopped and progesterone given, the temperature rose to above the basal level. Thus the temperature changes evoked by the sequential administration of estrogen and progestogen was the same as when each of these hormones was given without relation to the other.

Two experiments were carried out on six regularly menstruating women. It was found that, during the postovulatory phase, a single large intramuscular injection of alpha estradiol benzoate, given at midnight, caused a definite short dip in the temperature curve. A rise in basal body temperature, lasting no more than twenty-four hours, was obtained in these women, during the follicular phase of the cycle, by the injection of 50 mg. of progesterone in two equally divided doses at twelve-hour intervals.

From the foregoing experiments, it is demonstrated that progesterone is thermogenic, despite the presence of estrogen which normally lowers the temperature. This in turn supports the thesis that the biphasic temperature pattern of the ovulatory menstrual cycle is caused by the rhythmic production of estrogen and progestogen by the ovary.

HERBERT J. SIMON.

Malignancies

Dross, Raymond L., and Cutts, Frank B.: Myocardial Metastases From Carcinoma of the Cervix With Ventricular Tachycardia and Sudden Death, South. M. J. **42**: 1040, 1949.

In the case of carcinoma of the cervix with metastases to the right ventricle as reported, ventricular tachycardia and sudden death followed treatment of the primary tumor with radium. Metastasis to the heart is most unusual and where it does occur extension is usually by way of the lymphatics to the right side of the heart. The occurrence of cardiac arrhythmias in association with neoplatic disease anywhere in the body should arouse suspicion of metastatic cardiac involvement.

WILLIAM BICKERS.

Scott, Roger B., and Brack, C. Bernard: Attempted Heterologous Transplantation of Carcinoma of the Cervix, Bull. Johns Hopkins Hosp. **84**: 526, 1949.

In an effort to study the particular cells which make up carcinoma of the human cervix, twelve untreated and relatively late advanced cervical carcinomas were transplanted into the anterior chamber of a guinea pig's eye. None of the transplants took well but in two instances tiny islands of viable malignant tissue were found in the guinea pig's eye fifteen to twenty-two days after the original transplant. In one of these a spindle-cell type of tumor by original biopsy did generate an epithelial pearl. It is, however, the authors' conclusion that the heterologous transplant technique for the study of human malignant tissue is not applicable to carcinoma of the cervix. It may be that secondary infection or the ever-present fibrous scarring were factors responsible for the failure. L. M. HELLMAN.

Mammary Glands

Atkins, H. J. B.: The Effect of Endocrines on Fibroadenosis of the Breast, Brit. M. J. p. 750, April 30, 1949.

The effects of estrogens and androgens on the process known as fibroadenosis or "a painful nodular condition of the breast not due to bacteria, new growth or fat necrosis," was studied. Biopsies before and after treatment were taken and used as criteria of results. With estrogen, histologically, the fibroblastic reaction, the epitheliosis, and the adenosis all tended to increase. With androgen the process was reversed, and in a high percentage of cases, temporary improvement in signs and symptoms was noted. Many, however, tended to relapse after cessation of treatment. The most important disadvantage of androgen therapy was the arrhenomimetic changes. The author states that androgen therapy was of little value in the treatment of this disease because of the recurrence of symptoms and the undesirable side effects.

Menstruation, Dysmenorrhea

Davis, M. Edward, and Hulit, Bob Eugene: Changes in Circulating Eosinophils in Women During the Menstrual Cycle and Reproduction, J. Clin. Endocrinol. **9**: 714, 1949.

This study was undertaken to demonstrate the relationship between adrenal cortical function and the number of circulating eosinophiles. Eosinophile counts were done on 100 normal women during their reproductive years. It was found that there was a drop in the number of circulating eosinophiles at the time of ovulation (as indicated by a rise in body temperature) and that the number of eosinophiles was lower during the luteal phase than during the follicle phase.

Counts made on 300 normal pregnant women showed no change in the number of eosinophiles as pregnancy progressed. However, as there is a leucocytosis during pregnancy, there is a relative eosinopenia. The leucocytosis of pregnancy increases rapidly during labor, a peak being reached immediately post partum and returning to preparturition levels by the ninth postpartum day. During labor, an eosinopenia develops which progresses during the second and third stages until it is almost total in the immediate postpartum period. The eosinophile count returns to normal by the end of the third postpartum day. Thus the eosinophile count is more sensitive than the white count in its response to labor.

Eight patients subjected to elective cesarean section developed eosinopenia which lasted somewhat longer than in those who delivered through the pelvis. Two patients with eclamptic convulsions were studied and both developed a total eosinopenia during their seizures. Counts done on 10 patients who underwent various gynecologic operations showed a marked fall in the eosinophile count immediately postoperatively. The extent of the drop varied with the magnitude of the surgery.

The authors suggest that, in view of the fall in the circulating eosinophiles, at the time of ovulation, it is possible that the physiologic stress of ovulation may be more profound than has been thought previously. The relative eosinopenia of pregnancy which may become absolute during and immediately after labor, probably represents an increased adrenal cortical activity. The absolute eosinopenia during eclamptic seizures indicates the necessity for investigation of the adrenal cortical and pituitary activity and their relationship to eclampsia. The eosinopenia of surgical trauma is an indication of the natural adrenal cortical response. It has been shown by other authors that the injection of ACTH is followed by a prompt fall in the number of eosinophiles and a rise in the acid-creatinine ratio in the urine in normal subjects, while these effects are negligible in the presence of adrenal cortical failure. In addition, the administration of epinephrine to normal animals produces an increase in adrenal cortical activity, but there is no response if the animal has been hypophysectomized. Thus the number of circulating eosinophiles would seem to be an index to the presence of primary pituitary and adrenal disease. HERBERT J. SIMON.

Blaikley, J. B.: Menorrhagia of Emotional Origin, Lancet, p. 691, Oct. 15, 1949.

The author describes eight cases of menorrhagia without gross pelvic disease, in which detailed questioning revealed profound emotional disturbance often of psychosexual origin. On mental rehabilitation the menorrhagia disappeared rather promptly. Curettement was performed in only three of these patients, and endocrine studies in none.

It is suggested that most menorrhagias are of psychogenic origin if the endometrium is normal. Endometrial hyperemia and vasodilatation are responsible for heavy and prolonged bleeding. Shortening of the cycle is explained by psychogenic influences on the hypothalamus and thence on the pituitary. IRVING L. FRANK.

Miscellaneous

Collins, Harvey S., and Finland, Maxwell: Aureomycin Treatment of Urinary Tract Infection, Surg., Gynec. & Obst. 89: 43, 1949.

Sixteen patients with urinary tract infection were treated with aureomycin in doses of 0.5 Gm. twice a day for about one week. Fifteen of these patients had extremely chronic urinary tract disease and many had definite anatomical lesions of the kidney or urinary tract. The majority of organisms were sensitive to aureomycin. In general, the pyuria diminished markedly during therapy and disappeared entirely in about half the patients. Symptomatic relief occurred at the same time. Cultures usually became sterile during treatment but there was recurrence of the bacteria and in a few cases new bacteria followed cessation of treatment. Results of a permanent nature were infrequent. The authors felt that results were probably as good, if not better, than those usually obtained with sulfanilamide or streptomycin. Since most of the patients had previously proved refractory to these agents it was thought that aureomycin would prove a definite addition to the treatment of chronic urinary tract infection. L. M. HELLMAN.

Waller, R. K., and Waller, M.: Sensitizations to the Rh Factor in Negroes, J. Lab. & Clin. Med. 34: 1071, 1949.

The authors present a study of the Rh factor in their hospital clinic which has a preponderance of Negro patients. Their figures suggest that (a) the incidence of Rh negativity is lower in Negro than white patients; (b) the rate of sensitization was the same in both groups; (c) the incidence of erythroblastic infants appeared lower in the Negro group.

These observations are difficult to evaluate statistically because of the relatively small number of white patients in their group and the short hospital stay of their Negro patients which made adequate neonatal observation of the babies impossible.

S. B. GUSBERG.

Woodside, Moya: Sexual and Psychological Adjustment After Sterilization, West. J. Surg. 57: 600, 1949.

The physical and psychological adjustment of patients following sterilization has not received the attention which the subject merits. In the group of sterilized women under consideration here the indications for operation were medical and the procedure was either tubal ligation or bilateral salpingectomy. When this group of women was studied fourteen months following operation the general health had improved in approximately 50 per cent and deteriorated in 6 per cent. Menstruation was unchanged in 60 per cent, coitus was practiced more frequently in a small percentage of the patients, but otherwise there was little change in the physical behavior or the reaction pattern. It was in the psychological sphere that the greatest difference was observed. The fear of pregnancy having been removed, there was less anxiety and according to the author the individuals were happier. In those patients where the psychological attitude of the patient had deteriorated following the operation, the changes were ascribed by the author to neurotic personality and maladjustment in life situation. It is stated by the author that the results of operation would have been improved if it had been performed earlier in many patients. Convincing evidence is not presented to support most of the conclusions reached in this article. WILLIAM BICKERS.

Newborn

Rychener, R. O.: Retrolental Fibroplasia, Illinois M. J. 96: 299, 1949.

The author briefly reviews the literature concerning retrolental fibroplasia in premature infants and presents two cases of his own. He cites the incidence of approximately 12 per cent in premature infants under 3 pounds and emphasizes the futility of any known treatment. He adds to the generally gloomy picture by speculating about the etiology of this disease without any specific data to support these contentions. S. B. GUSBERG.

Lucia, S. P., and Hunt, M. L.: Hemolytic Disease of the Newborn. II. An Analysis of Maternal Ante-Partum Factors in a Sample of Sensitized Rh-Negative Women in Relation to the Clinical Condition of Their Offspring, J. Lab. & Clin. Med. 35: 28, 1950.

An analysis of 198 pregnancies in sensitized Rh-negative patients is presented in an attempt to evaluate the factors that might help predict the fetal outcome. Of these patients, 96 gave birth to infants with hemolytic disease and 102 bore normal infants. Of the total group there were 172 Rh-positive infants giving an incidence of 56 per cent hemolytic disease in this group; of these 96, 48 died.

The most important factor with respect to damaged infants appeared to be higher amounts of maternal Rh antibodies in albumin diluent (''incomplete'' antibodies) than in saline, followed in order by the other factors: (2) considerable amounts of Rh antibodies in maternal serum during the last month; (3) appearance of antibodies earlier than 10 weeks before term; (4) the presence of Rh antibodies on all successive testings after their first appearance; (5) the presence of ABO compatibility between mother and child.

The complexity of assaying these factors in an individual case is evident, but the authors state that hemolytic disease never occurred in their group if 2 or more of these factors were absent. S. B. GUSBERG.

Boorman, K. E., Dodd, B. E., and Trinick, R. H.: Haemolytic Disease of the Newborn Due to Anti-A Antibodies, Lancet (London), p. 1088, June 25, 1949.

The presence of immune anti-A and anti-B agglutinins in maternal serum, even in high titer, does not identify the cause of hemolysis in the fetus, because such agglutinins are produced in most instances of heterospecific blood group pregnancy even when the infant is normal. Moreover, sensitization to each of the members of the complex Rh

system should be ruled out in suspect cases. Good evidence for the diagnosis is the demonstration of abnormally rapid elimination from the infant circulation of transfused blood cells containing the blood group antigen in question.

This demonstration was carried out by the transfusion of a washed mixture of group A Rh-positive cells and group O Rh-negative cells to an anemic group A Rh-negative infant. Almost all of the transfused group A cells and some of the infant's own group A cells were destroyed, despite normal survival of the group O cells.

In another case ending fatally, the responsibility of this process was shown by the demonstration of blocking anti-A antibodies in eluates of various fetal tissues obtained at autopsy. IRVING L. FRANK.

Illingworth, R. S., Harvey, C. C., and Gin, Shan-Yah: Relation of Birth Weight to Physical Development in Childhood, Lancet (London), p. 598, Oct. 1, 1949.

This paper presents a statistical comparison of the heights and weights of 2,400 children in relation to their recorded birth weights. At all ages there was a well-marked parallelism between physical development and birth weight, subject to considerable variation in individual children. The study does not attempt to evaluate, as such, the influences of maternal nutrition and health, prematurity, and genetic variability. IRVING L. FRANK.

Martyn, G.: The Relation of Staphylococcus Pyogenes to Infantile Diarrhoea and Vomiting, Brit. M. J., p. 1146, Nov. 19, 1949.

Bacteriological studies of the stools of 119 infants suffering from diarrhea and vomiting and of 122 controls is recorded. Using a highly selective medium *Staphylococcus pyogenes* was isolated from 44.5 per cent of the former as compared to 46 per cent of controls. In most instances it is probable that the organism was present in small numbers. The phage types were essentially the same in strains recovered from both the ill and control infants. Sensitivity to penicillin and streptomycin was not different statistically in the two groups. A food poisoning type of staphylococcus was found five times in each group.

The authors concluded that the presence of staphylococcus in the stools of infants with diarrhea and vomiting does not seem to indicate that the organism bears any causal relationship to the disease. R. GORDON DOUGLAS.

Pregnancy, Physiology

Kapeller-Adler, R.: Histamine Metabolism During Pregnancy, Lancet, p. 745, Oct. 22, 1949.

Histamine is a normal constituent of blood, whereas histaminase is found in blood only during human pregnancy. This study was made on blood samples drawn from eight nonpregnant women, and from ninety-one women in various stages and conditions of pregnancy, parallel determinations being made of serum histaminase, histamine in blood cells, and histamine in plasma.

Histaminase activity was not demonstrable in nonpregnant women, but was strong in all cases of pregnancy, somewhat higher levels being encountered from the twenty-third to thirty-fifth week of gestation. In mild pre-eclampsia the level was not altered, but in severe pre-eclampsia, threatened abortion, and antepartum hemorrhage it was distinctly deceased. Histaminase activity declined slightly during prolonged labor, and disappeared during the puerperium. It is generally accepted that histaminase is produced in the placenta, and hence any degenerative change in the placenta may lead to a fall in serum histaminase.

Blood histamine is concentrated largely in the cells, and only small amounts are found occasionally in plasma of nonpregnant women. In normal pregnancy histamine distribution is unaltered, but in mild and severe pre-eclampsia, and in pregnancy pyelitis, plasma histamine

rises distinctly. Only in severe pre-eclampsia is there a significant drop in blood-cell histamine, sometimes to a level below that of the plasma. It is suggested that during pregnancy an alteration in the metabolism of histamine permits its free passage from cells to tissue fluids, and that serum histaminase is present to protect against potential histamine intoxication.

IRVING L. FRANK.

Swyer, G. I. M.: Clinical Value of Pregnanediol Assays, Brit. M. J., p. 830, Oct. 15, 1949.

In this paper an attempt is made to evaluate the position of free pregnanediol assay quantitatively in first morning specimens of urine where the technique employed was practical from a clinical point of view and could be done in a few hours. It is pointed out that tedious determinations requiring several days and total daily urines may be of value from a research standpoint but are impractical for routine clinical use. Two techniques were employed; method I, a modification of the Guterman technique, and method II, which was described by Sommerville, Marrian, and Kelar. The latter method was considered the more satisfactory but in an analysis of 858 assays there is a considerable degree of overlap of values for pregnant and nonpregnant urines by both procedures.

Both of the above methods were employed and compared to the Friedman test and the ultimate clinical answer to determine its value as a diagnostic test for pregnancy. With employment of method I, false positives were rare but false negatives were frequent, and the test was accurate in only 67.3 per cent of cases from a positive point of view. Method II gave a correct result in 82 per cent of cases but the number of false positives was considerably increased. Obviously, the conclusion is reached that irrespective of the results of previously published data neither method can be considered satisfactory as a diagnostic test for pregnancy.

Forty cases of threatened abortion were employed to determine the value of the test from a prognostic point of view in threatened abortion. Pregnanediol determinations were in general higher when pregnancy continued as compared to when abortion occurred. However, there was a considerable overlap of values and a correct prognosis was made in only 29 out of the 40 cases.

The test was employed in 10 patients in whom induction of labor was attempted to determine its value in prognosticating success. This is based on a reported fall in pregnanediol excretion just before the onset of labor. It was concluded that the fate of a given patient could not be determined by pregnanediol assay.

A number of different complications of pregnancy were studied. In hydatidiform mole, excretion was nil, but in missed abortion, hemorrhage, polycystic ovaian disease, and dystocia no significant results were obtained.

In conclusion it is stated that this test has relatively little to offer the practicing clinician. The author believes that this is due to variability of pregnanediol excretion both in the same and different patients rather than to inaccuracy of the methods employed. He is also of the opinion that pregnanediol excretion is not necessarily closely related to the progesterone level of the blood.

R. GORDON DOUGLAS.

Bryce-Smith, R., Seward, E. H., Williams, E. A., and Williams, E. O.: Continuous Spinal Block in Puerperal Hypertensive Encephalopathy With Anuria, Lancet (London), p. 831, Nov. 5, 1949.

The authors report a case of postpartum eclampsia with a hypertension reaching 210/140, anuria, uremia, and symptoms of cerebral irritation. Deep sedation failed to lower blood pressure, and a continuous caudal block was given for twenty-two hours. Since there was little effect on the blood pressure, and signs of incipient heart failure appeared, a continuous spinal block was established and maintained for four and one-half days. During this time there was a spectacular improvement in general condition, the blood pressure was reduced to levels about 140/80, and urinary output gradually rose to about 2 L. daily. Several days after treatment was discontinued the patient died suddenly, death being attributed to irreversible adrenal and myocardial damage.

IRVING L. FRANK.

Gilbert, J. A. L.: The Association of Maternal Obesity, Large Babies, and Diabetes, Brit. M. J., p. 702, April 23, 1949.

Twenty-one women with obstetrical histories of unexplained abortions, miscarriages, intrauterine deaths, stillbirths, neonatal deaths, and the birth of babies weighing 10 pounds or more were admitted to the hospital for investigation. Six of these patients were found to be diabetic. All six were grossly obese and five had babies weighing 10 pounds or more.

Evidence is brought forward to show a correlation between progressive maternal obesity, the birth of unusually large babies, and ensuing maternal diabetes. It is suggested that an excessive secretion of the growth factor during pregnancy may account for the associated phenomenon.

R. Gordon Douglas.

Sheldon, J. H.: Maternal Obesity, Lancet (London), p. 869, Nov. 12, 1949.

This study is a detailed analysis of the case histories of 40 women who exhibited a 75 per cent to 125 per cent gain over their weights at marriage. In some cases weight gain was an abrupt response to a particular pregnancy; in others it was a sum of increments following each pregnancy. The onset of weight gain came during pregnancy in some, and immediately following pregnancy in others. From his analysis of these variables and of personal and family histories, the author deduces that some type of hypothalamic disturbance is responsible for the obesity, in analogy to the weight gain which occurs in animals after operative damage to the hypothalamus, independent of pituitary status. In some patients this hypothalamic change is followed by an increase in anterior pituitary function, resulting in large babies, high rate of fetal loss, and possibly in late diabetes.

Irving L. Frank.

Venereal Diseases

Blum, Paul: The Ovary and Syphilis: Practical Considerations, Monde méd., Paris **59**: 218, 1949.

The author presents a discussion of possible clinical manifestations of syphilitic oophoritis, stressing functional ovarian disturbances. He noted sporadic intermenstrual leucorrhea in patients with secondary syphilis. A syndrome of recurring episodes of cramping abdominal pain, beginning one or two days prior to the onset of menstruation, and apparently permanently relieved by antisyphilitic therapy, was observed in several instances. Amenorrhea and oligomenorrhea were routinely noted in both early and late syphilis, but rarely in the secondary form of the disease. The author states that both tertiary and congenital syphilis may bring about a true premature menopause characterized by neurocirculatory disturbances, regression of secondary sex characters, and atrophic genital changes such as kraurosis vulvae and leucoplakia. Congenital syphilitic oophoritis may account for some cases of delayed puberty and primary amenorrhea, although there are reported cases of precocious puberty in congenitally syphilitic girls. The author believes that congenital syphilis is a frequent cause of sterility. He urges that all syphilitic women with clinical signs of endocrine disturbance be carefully studied both before and after specific therapy in order to evaluate the possibility of ovarian involvement, since he believes syphilitic oophoritis to be considerably more common than has been thought to be the case in the past.

Douglas M. Haynes.

Correspondence

Irradiation for Sterility

To the Editor:

In 1948 I was able to report on the birth of a son to a girl born of a mother who was irradiated 23 years before for sterility. Now I am able to report a second instance, of a son born to a son who was born to a mother irradiated 23 years ago for sterility. The data in this case are as follows:

Mrs. M. M. was referred to me for x-ray treatment for sterility on Feb. 22, 1927. At that time she was 24 years old. Her menstruation began at 12½ years of age, and was always irregular, with periods occurring at 2- to 3-month intervals. She married at 21 and used no contraceptives. After two years of marriage, not becoming pregnant, she sought medical advice. In 1925, a curettage was performed but this and subsequent glandular medication therapy failed to alleviate the sterility. The husband was normal and potent. Her last menstruation before x-ray therapy was advised occurred in March, 1926, eleven months prior to x-ray therapy. Physical examination revealed no abnormalities; she was somewhat stout and rather short. The gynecologic anatomy was reported as normal. X-ray therapy was administered in the usual manner, in the method devised by and previously reported by me, the rays being directed to the ovaries and the pituitary, between Feb. 22 and March 7, 1927.

She responded well to treatment, menstruated, and became pregnant, and gave birth to a normal baby boy on Nov. 18, 1928. She subsequently gave birth to three more children, a girl on Aug. 28, 1930, another girl on Aug. 8, 1934, and a fourth child, a girl, on July 18, 1940.

The boy born on Nov. 18, 1928, developed normally and served in the United States Army during World War II. In 1949, he married and now, on March 10, 1950, his wife gave birth to a normal boy weighing 8 pounds, 3½ ounces.

Whereas animal experimentation results are readily achieved in the laboratory, to study the effects of irradiation on subsequent human generations following x-ray therapy to the mothers is not possible before the lapse of approximately 20 years following the birth of the first generation offspring of such irradiated mothers.

This birth of a normal child to a normal child previously born to a mother irradiated for sterility again supports my pronouncement, previously published in this JOURNAL in 1928, namely, that irradiation when properly administered for the treatment of sterility is harmful neither to the mother nor to the offspring, and I can add now with equal assurance, to the subsequent offspring of such offspring. Moreover, an experience of over twenty-five years permits me to add that such irradiation has proved a valuable therapeutic procedure for the treatment of female sterility.

Because of the recent adverse criticisms leveled at irradiation and the keen interest in its genetic effects, this communication is submitted for the attention of your readers.

IRA I. KAPLAN, M.D.

755 PARK AVENUE.

Item

American Board of Obstetrics and Gynecology

The following physician is to be included in the list of diplomates of this Board: John J. McCarthy, M.D., 1001 79th Street, North Bergen, New Jersey; born 1906; received M.D. from Georgetown University in 1931.

PAUL TITUS, M.D.,
SECRETARY.

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2. Henderson, V. E.: Canad. M. A. J., 35:636-637, 1936
3. Gunther, Lewis: U. S. Nav. Med. Bull., 44:300, 1945

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